```
=> fil drugu jic pascal biotechno biosis esbio biotechds confsci dissabs scisearch;
d que l95
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Inventor search

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L88           60 SEA PONIKAU J?/AU
L89         4318 SEA KITA H?/AU
L90          173 SEA SHERRIS D?/AU
L91        85103 SEA EOSINOPHIL#
L92       115320 SEA (DRUG# OR COMPOUND#)(2A)(SCREEN? OR EVALUAT? OR DISCOVER?)

L93         1652 SEA FUNG##(2A) ANTIGEN#
L94       281222 SEA ALTERNARIA OR CANDIDA OR ASPERGILLUS OR CLADOSPORI?
L95           28 SEA L88 AND L89 AND L90 AND (L91 OR L92 OR L93 OR L94)


=> fil medl; d que l21; fil embase; d que l55; fil wpix;d que l69; fil capl; d que
l1; d que l17; s l1,l17
FILE 'MEDLINE' ENTERED AT 14:31:36 ON 28 SEP 2006

 FILE LAST UPDATED: 27 Sep 2006 (20060927/UP). FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 is now (26 Feb.) available. For details
 on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
```

Searched by Barb O'Bryen, STIC 2-2518

http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

L18	18	SEA FILE=MEDLINE ABB=ON	PONIKAU J?/AU
L19	396	SEA FILE=MEDLINE ABB=ON	KITA H?/AU
L20	69	SEA FILE=MEDLINE ABB=ON	SHERRIS D?/AU
L21	9	SEA FILE=MEDLINE ABB=ON	L18 AND L19 AND L20

FILE 'EMBASE' ENTERED AT 14:31:37 ON 28 SEP 2006

FILE COVERS 1974 TO 28 Sep 2006 (20060928/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

EMBASE is now updated daily. SDI frequency remains weekly (default) and biweekly.

This file contains CAS Registry Numbers for easy and accurate substance identification.

L42	20	SEA FILE=EMBASE ABB=ON	PONIKAU J?/AU
L43	410	SEA FILE=EMBASE ABB=ON	KITA H?/AU
L44	59	SEA FILE=EMBASE ABB=ON	SHERRIS D?/AU
L55	10	SEA FILE=EMBASE ABB=ON	L42 AND L43 AND L44

FILE 'WPIX' ENTERED AT 14:31:37 ON 28 SEP 2006

FILE LAST UPDATED: 27 SEP 2006 <20060927/UP>
MOST RECENT DERWENT UPDATE: 200662 <200662/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE, PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://scientific.thomson.com/support/patents/coverage/latestupdates/

>>> PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
http://www.stn-international.de/stndatabases/details/ipc_reform.html and
http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf <<<

>>> FOR FURTHER DETAILS ON THE FORTHCOMING DERWENT WORLD PATENTS

INDEX ENHANCEMENTS PLEASE VISIT:
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<
'BI ABEX' IS DEFAULT SEARCH FIELD FOR 'WPIX' FILE

L66 4 SEA FILE=WPIX ABB=ON PONIKAU J?/AU
L67 338 SEA FILE=WPIX ABB=ON KITA H?/AU
L68 9 SEA FILE=WPIX ABB=ON SHERRIS D?/AU
L69 3 SEA FILE=WPIX ABB=ON L66 AND L67 AND L68

FILE 'CAPLUS' ENTERED AT 14:31:38 ON 28 SEP 2006
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FILE COVERS 1907 - 28 Sep 2006 VOL 145 ISS 14
FILE LAST UPDATED: 27 Sep 2006 (20060927/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE

L1 1 SEA FILE=CAPLUS ABB=ON US2005-505379/AP

L14 10 SEA FILE=CAPLUS ABB=ON PONIKAU J?/AU
L15 1790 SEA FILE=CAPLUS ABB=ON KITA H?/AU
L16 29 SEA FILE=CAPLUS ABB=ON SHERRIS D?/AU
L17 6 SEA FILE=CAPLUS ABB=ON L14 AND L15 AND L16

L108 6 (L1 OR L17)

=> => dup rem l108,l21,l69,l55,l95
FILE 'CAPLUS' ENTERED AT 15:10:41 ON 28 SEP 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE 'MEDLINE' ENTERED AT 15:10:41 ON 28 SEP 2006

FILE 'WPIX' ENTERED AT 15:10:41 ON 28 SEP 2006

PROCESSING COMPLETED FOR L108
PROCESSING COMPLETED FOR L21
PROCESSING COMPLETED FOR L69
PROCESSING COMPLETED FOR L55
PROCESSING COMPLETED FOR L95
L109 17 DUP REM L108 L21 L69 L55 L95 (39 DUPLICATES REMOVED)
ANSWERS '1-6' FROM FILE CAPLUS
ANSWERS '7-11' FROM FILE MEDLINE
ANSWER '12' FROM FILE WPIX
ANSWER '13' FROM FILE EMBASE
ANSWERS '14-16' FROM FILE BIOSIS
ANSWER '17' FROM FILE SCISEARCH

=> d ibib ed abs 1-17

L109 ANSWER 1 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2006:164371 CAPLUS
DOCUMENT NUMBER: 144:208478
TITLE: Detecting Alternaria fungi in human samples using immunoassays
INVENTOR(S): **Kita, Hirohito**; Squillace, Diane; **Sherris, David A.**; **Ponikau, Jens**; Swanson, Mark
PATENT ASSIGNEE(S): Mayo Foundation for Medical Education and Research, USA
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006020915	A2	20060223	WO 2005-US28821	20050812
WO 2006020915	A3	20060629		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,

GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-601427P P 20040812

ED Entered STN: 23 Feb 2006

AB Methods and materials involved in detecting fungi in human samples are provided herein. A method for detecting a fungal organism, especially Alternaria alternata in a sample from a mammal, wherein said fungal organism produces a fungal antigen comprises: (a) contacting said sample with an antibody in the presence of immobilized fungal antigens under conditions wherein fungal antigens present within said sample compete with said immobilized fungal antigens for binding to said antibody, and (b) detecting the level of competition between fungal antigens within said sample and said immobilized antigens by determining the level of formation of antibody-immobilized fungal antigen complexes, wherein the presence of said competition indicates that said nasal sample contains said fungal organism.

L109 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 4

ACCESSION NUMBER: 2005:704902 CAPLUS

DOCUMENT NUMBER: 144:486996

TITLE: Striking deposition of toxic eosinophil major basic protein in mucus: Implications for chronic rhinosinusitis

AUTHOR(S): **Ponikau, Jens U.; Sherris, David A.** ; Kephart, Gail M.; Kern, Eugene B.; Congdon, David J.; Adolphson, Cheryl R.; Springett, Margaret J.; Gleich, Gerald J.; **Kita, Hirohito**

CORPORATE SOURCE: Department of Otorhinolaryngology-Head and Neck Surgery, Mayo Clinic, Rochester, MN, USA

SOURCE: Journal of Allergy and Clinical Immunology (2005), 116(2), 362-369
CODEN: JACIBY; ISSN: 0091-6749

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 09 Aug 2005

AB Background: The mechanisms by which eosinophilic inflammation damages the epithelium and contributes to recurrent acute exacerbations in chronic rhinosinusitis (CRS) have not been fully elucidated. Objective: We tested the hypotheses that eosinophils deposit toxic major basic protein (MBP) in the mucus and that MBP reaches concns. able to damage the sinonasal epithelium. Methods: Tissue specimens with mucus attached to the tissue were carefully collected from 22 patients with CRS and examined by using immunofluorescence staining for MBP. This immunofluorescence was digitally analyzed to determine the area covered by MBP and the intensity of the staining (estimating MBP concentration). Levels of MBP in exts. from nasal mucus were quantitated by means of RIA. Results: Heterogeneous eosinophilia was evident within tissue and mucus specimens. All tissue specimens showed intact eosinophils, but diffuse extracellular MBP deposition, as a marker of eosinophil degranulation, was rare. In contrast, all mucus specimens showed diffuse MBP throughout and abundant diffuse extracellular MBP

deposition within clusters of eosinophils. Digitized analyses of MBP immunofluorescence revealed increased area coverage (P < .0001) in mucus compared with that seen in tissue. Estimated concns. of MBP within the clusters suggested toxic levels. MBP concns. in mucus extract reached 11.7 μg/mL; MBP was not detectable in healthy control subjects. Conclusion: In patients with CRS, eosinophils form clusters in the mucus where they release MBP, which is diffusely deposited on the epithelium, a process not observed in the tissue. Estimated MBP levels far exceed those needed to damage epithelium from the luminal side and could predispose patients with CRS to secondary bacterial infections.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L109 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2005:4639 CAPLUS
DOCUMENT NUMBER: 142:348494
TITLE: Treatment of chronic rhinosinusitis with intranasal amphotericin B: A randomized, placebo-controlled, double-blind pilot trial
AUTHOR(S): **Ponikau, Jens U.; Sherris, David A.** ; Weaver, Amy; **Kita, Hirohito**
CORPORATE SOURCE: Department of Otorhinolaryngology-Head and Neck Surgery, Mayo Clinic Rochester, Rochester, MN, 55905, USA
SOURCE: Journal of Allergy and Clinical Immunology (2005), 115(1), 125-131
CODEN: JACIBY; ISSN: 0091-6749
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 04 Jan 2005
AB Chronic rhinosinusitis (CRS) is one of the most common chronic diseases. Its etiol. is unknown, and there is a paucity of effective medical treatments. We tested the hypothesis that intranasal antifungal treatment improves the objective computed tomog. (CT) findings (inflammatory mucosal thickening), nasal endoscopy stages, and symptoms of CRS. A randomized, placebo-controlled, double-blind, single-center trial used amphotericin B to treat 30 randomly selected patients with CRS. Patients were instructed to instill 20 mL amphotericin B (250 μg/mL) or placebo to each nostril twice daily for 6 mo. The primary outcome was a quant. reduction in inflammatory mucosal thickening on CT scans of a standardized coronal cut. Secondary outcome measures were endoscopic scores, patient symptom scores, and levels of intranasal inflammatory mediators. Twenty-four patients completed the 6 mo of treatment. Patients receiving amphotericin B achieved a relative reduction in the percentage of mucosal thickening on CT scans (n = 10; -8.8%) compared with placebo (n = 14; +2.5%; P = .030). Likewise, the changes in the endoscopic scores improved in the amphotericin B group compared with placebo (P = .038). Between-group comparisons of the changes in the intranasal mucus levels of eosinophil-derived neurotoxin showed a reduction in the amphotericin B group and an increase in the placebo group (P = .046); levels of IL-5 showed similar tendencies (P = .082). Intranasal amphotericin B reduced inflammatory mucosal thickening on both CT scan and nasal endoscopy and decreased the levels of intranasal markers for eosinophilic inflammation in patients with CRS.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L109 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 2004:1044013 CAPLUS

DOCUMENT NUMBER: 142:238316
TITLE: Chronic rhinosinusitis: An enhanced immune response to ubiquitous airborne fungi
AUTHOR(S): Shin, Seung-Heon; **Ponikau, Jens U.**; **Sherris, David A.**; Congdon, David; Frigas, Evangelo; Homburger, Henry A.; Swanson, Mark C.; Gleich, Gerald J.; **Kita, Hirohito**
CORPORATE SOURCE: Division of Allergic Diseases and Department of Internal Medicine, Univ. Buffalo, The State Univ. New York, USA
SOURCE: Journal of Allergy and Clinical Immunology (2004), 114(6), 1369-1375
CODEN: JACIBY; ISSN: 0091-6749
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 06 Dec 2004
AB Chronic rhinosinusitis (CRS) is one of the most common long-term illnesses in the United States. The etiol. of CRS is unknown, and no effective treatment has been established. We investigated the hypothesis that abnormal immunol. responses to ubiquitous airborne fungi contribute to the pathogenesis of this disease. The proliferative and cytokine responses of PBMCs to exts. from 4 common airborne fungi-including Alternaria, Aspergillus, Cladosporium, and Penicillium-were examined by in vitro culture. Serum specimens were tested for specific IgE and IgG to these fungi. PBMCs from approx. 90% of the patients with CRS, but not those from normal individuals, produced both IL-5 and IL-13 when exposed to Alternaria. Furthermore, PBMCs from patients with CRS produced significantly more IFN-γ than PBMCs from normal individuals in response to Alternaria (median, 553 pg/mL vs. 98 pg/mL). Levels of serum IgG antibodies to Alternaria and Cladosporium were clearly increased in patients with CRS compared with normal individuals. Less than 30% of the patients with CRS had specific IgE antibodies to Alternaria or Cladosporium. The increased humoral (serum IgG) response strongly correlated with the increased cellular (IL-5 production) response to Alternaria. Patients with CRS show exaggerated humoral and cellular responses, both T1 and T2 types, to common airborne fungi, particularly Alternaria. The anomalous immune and inflammatory responses to ubiquitous fungi may explain the chronicity of airway inflammation in CRS.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RÈ FORMAT

L109 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 2003:719705 CAPLUS
DOCUMENT NUMBER: 139:229274
TITLE: Fungal antigens and eosinophil activity
INVENTOR(S): **Ponikau, Jens**; **Kita, Hirohito**; **Sherris, David A.**
PATENT ASSIGNEE(S): Mayo Foundation for Medical Education and Research, USA
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003075005	A1	20030912	WO 2003-US6380	20030228

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2003219979	A1	20030916	AU 2003-219979	20030228
US 2006165732	A1	20060727	US 2005-505379	20050727 <--
PRIORITY APPLN. INFO.:			US 2002-361211P	P 20020301
			US 2003-447840P	P 20030213
			WO 2003-US6380	W 20030228

ED Entered STN: 14 Sep 2003

AB The authors disclose T cell activation, eosinophil activation, and degranulation in response to fungal antigens. In one example, lymphocytes from patients with chronic rhinosinusitis were shown to release interleukin-5 in response to Alternaria and Candida exts. In a second example, Alternaria antigens were shown to induce activation and degranulation of eosinophils. The invention also provides animals having a fungal antigen-induced eosinophilic response as well as methods of making such animals and method of using such animals to identify compds. that inhibit an eosinophilic response in an animal.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L109 ANSWER 6 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 10

ACCESSION NUMBER: 2003:59337 CAPLUS
DOCUMENT NUMBER: 138:117292
TITLE: Intranasal antifungal treatment in 51 patients with chronic rhinosinusitis
AUTHOR(S): **Ponikau, Jens U.; Sherris, David A.** ; **Kita, Hirohito**; Kern, Eugene B.
CORPORATE SOURCE: Department of Otorhinolaryngology-Head and Neck Surgery, Mayo Clinic Rochester, Rochester, USA
SOURCE: Journal of Allergy and Clinical Immunology (2002), 110(6), 862-866
CODEN: JACIBY; ISSN: 0091-6749
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

ED Entered STN: 26 Jan 2003

AB Background: Chronic rhinosinusitis (CRS) is the most common chronic disease that is frequently refractory to treatment. Objective: We sought to establish the safety and demonstrate the clin. efficacy of intranasal antifungal drug therapy in patients with CRS in a pilot trial. Methods: A prospective open-label trial used amphotericin B as a medical treatment in 51 randomly selected patients with CRS. The antifungal agent was applied intranasally as 20 mL of a 100 μg/mL solution twice daily. The outcome was measured by using their symptoms and by using an endoscopic scoring, system in all patients. In addition, pretreatment and posttreatment coronal computed tomog. scans of the nose and sinuses were available for evaluation in 13 patients. Results: By using amphotericin B, improvement of sinusitis symptoms was observed in 38 (75%) of 51 patients. Endoscopically, 18 (35%) of 51 patients became disease free, and an addnl. 20 (39%) of 51 bad improvement of at least one stage (P <.001). No effect was seen in 13 (25 %) of 51 patients. The available computed tomog. scans before and after treatment demonstrated a significant reduction in the

inflammatory mucosa thickening that had occluded the paranasal sinuses (P <.0001 in maxillary sinus). Conclusion: This open-label pilot trial demonstrates that direct mucoadministration of an antifungal drug appears to be both safe and effective in the treatment of patients with CRS. Therefore controlled and blinded trials are indicated to clarify the novel role of intranasal antifungal drugs in the treatment of CRS.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L109 ANSWER 7 OF 17 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2006369653 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16785589
TITLE: The role of ubiquitous airborne fungi in chronic rhinosinusitis.
AUTHOR: **Ponikau Jens U; Sherris David A;** Kephart Gail M; Adolphson Cheryl; **Kita Hirohito**
CORPORATE SOURCE: Department of Otorhinolaryngology, University at Buffalo, The State University of New York, Buffalo, NY, USA.. jponikau@buffailo.edu
CONTRACT NUMBER: AI 49235 (NIAID)
AI 50494 (NIAID)
SOURCE: [redacted] Vol. 30, No. 3, pp. 187-94. Ref: 41
Journal code: 9504368. ISSN: 1080-0549.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200607
ENTRY DATE: Entered STN: 21 Jun 2006
Last Updated on STN: 29 Jul 2006
Entered Medline: 28 Jul 2006

ED Entered STN: 21 Jun 2006
Last Updated on STN: 29 Jul 2006
Entered Medline: 28 Jul 2006

AB Chronic rhinosinusitis (CRS) is a confusing disease for both allergists and otorhinolaryngologists, partly because of its poorly understood pathophysiology and partly because of its limited treatment options. Several recent reports have provided evidence for a better understanding of the etiology and the relationship of CRS to airborne fungi-especially to Alternaria. First, the development of novel methods enables detection of certain fungi in mucus from the nasal and paranasal sinus cavities. Second, a non-IgE-mediated immunological mechanism for reactivity of patients with CRS to certain common fungi has been described. Third, these fungi are surrounded by eosinophils in vivo, suggesting that they are targeted by eosinophils. Finally, the preliminary results of studies using antifungal agents to treat patients with CRS are promising. Overall, these recent discoveries provide a logical mechanism for the pathophysiology of CRS, and they also suggest promising avenues for treatment of CRS with antifungal agents.

L109 ANSWER 8 OF 17 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2005540774 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16216172
TITLE: The role of ubiquitous airborne fungi in chronic rhinosinusitis.
AUTHOR: **Ponikau Jens U; Sherris David A;** Kephart Gail M; Adolphson Cheryl; **Kita Hirohito**
CORPORATE SOURCE: Department of Otorhinolaryngology, University at Buffalo,

The State University of New York, 3C41 Millard Fillmore Hospital, 3 Gates Circle, Buffalo, NY 14209, USA..
jponikau@buffalo.edu
CONTRACT NUMBER: AI 49235 (NIAID)
AI 50494 (NIAID)
SOURCE: Current allergy and asthma reports, (2005 Nov) Vol. 5, No. 6, pp. 472-6. Ref: 41
Journal code: 101096440. ISSN: 1529-7322.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200601
ENTRY DATE: Entered STN: 12 Oct 2005
Last Updated on STN: 26 Jan 2006
Entered Medline: 25 Jan 2006
ED Entered STN: 12 Oct 2005
Last Updated on STN: 26 Jan 2006
Entered Medline: 25 Jan 2006
AB Chronic rhinosinusitis (CRS) is a confusing disease for both allergists and otorhinolaryngologists, partially due to its poorly understood pathophysiology and partially due to its limited treatment options. Several recent reports now provide evidence for a better understanding of the etiology and the relationship of CRS to airborne fungi, especially to Alternaria. First, the development of novel methods enables detection of certain fungi in mucus from the nasal and paranasal sinus cavities. Second, a non-immunoglobulin E-mediated immunologic mechanism for reactivity of CRS patients to certain common fungi has been described. Third, these fungi are surrounded by eosinophils in vivo, suggesting that they are targeted by eosinophils. Fourth, the preliminary results of studies using antifungal agents to treat patients with CRS are promising. Overall, these recent discoveries provide a logical mechanism for the pathophysiology of CRS, and they also suggest promising avenues for treatment of CRS with antifungal agents.

L109 ANSWER 9 OF 17 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2003532326 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14610473
TITLE: Features of airway remodeling and eosinophilic inflammation in chronic rhinosinusitis: is the histopathology similar to asthma?.
AUTHOR: **Ponikau Jens U; Sherris David A;** Kephart Gail M; Kern Eugene B; Gaffey Thomas A; Tarara James E; **Kita Hirohito**
CORPORATE SOURCE: Department of Otolaryngology-Head and Neck Surgery, Mayo Clinic, Rochester, Minn 55905, USA.
CONTRACT NUMBER: AI 49235 (NIAID)
AI 50494-P3 (NIAID)
SOURCE: The Journal of allergy and clinical immunology, (2003 Nov) Vol. 112, No. 5, pp. 877-82.
Journal code: 1275002. ISSN: 0091-6749.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 13 Nov 2003
Last Updated on STN: 20 Dec 2003
Entered Medline: 19 Dec 2003

ED Entered STN: 13 Nov 2003
Last Updated on STN: 20 Dec 2003
Entered Medline: 19 Dec 2003

AB BACKGROUND: Asthma and chronic rhinosinusitis (CRS) coexist clinically in >50% of patients with CRS. Although epithelial damage and basement membrane thickening are well-known features of airway remodeling in asthma, they have not been described in CRS. OBJECTIVE: In this study, we tested the hypothesis that histopathologic features of asthma, namely, the chronic eosinophilic inflammation, epithelial damage, and basement membrane thickening of the airway mucosa, are also present in sinonasal specimens from patients with CRS. METHODS: We examined histologic specimens from 22 randomly selected patients with refractory CRS undergoing endoscopic sinus surgery and 4 healthy control subjects. The shedding of the epithelium and basement membrane thickening were evaluated by 3 independent observers' scores of hematoxylin-and-eosin staining. Eosinophilic inflammation was monitored with immunohistochemistry for eosinophil major basic protein. A novel, computerized method objectively analyzed confocal microscopic images of major basic protein immunofluorescence to determine areas with the least and most inflammation per specimen. RESULTS: Specimens from all patients with CRS (22/22) revealed epithelial damage (shedding) and basement membrane thickening. Strikingly heterogeneous eosinophilic inflammation, which did not differ between allergic and nonallergic patients, was detected in all patients with CRS and was absent in all healthy control subjects. CONCLUSION: The histopathologic findings of asthma, namely, heterogeneous eosinophilic inflammation and features of airway remodeling, are also present in CRS. These findings, coupled with the common clinical coexistence of both diseases, suggest that the same pathologic disease process is manifest as CRS in the sinonasal tissue and as asthma in the lower airway.

L109 ANSWER 10 OF 17 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 2003056515 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12567086
TITLE: The chemotactic behavior of eosinophils in patients with chronic rhinosinusitis.
AUTHOR: Wei Julie L; **Kita Hirohito; Sherris David A**; Kern Eugene B; Weaver Amy; **Ponikau Jens U**
CORPORATE SOURCE: Department of Otorhinolaryngology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA.
SOURCE: The Laryngoscope, (2003 Feb) Vol. 113, No. 2, pp. 303-6. Journal code: 8607378. ISSN: 0023-852X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 5 Feb 2003
Last Updated on STN: 22 Feb 2003
Entered Medline: 21 Feb 2003

ED Entered STN: 5 Feb 2003
Last Updated on STN: 22 Feb 2003
Entered Medline: 21 Feb 2003

AB OBJECTIVE: To characterize peripheral eosinophil migration in patients with chronic rhinosinusitis in the presence of nasal mucin and nasal tissue extracts. STUDY DESIGN: Prospective, controlled, ex-vivo. METHODS: Peripheral blood eosinophils, nasal mucin, and nasal tissue were harvested at the time of sinus surgery in 10 patients, as well as obtained in 10 healthy control subjects. Extracts were prepared from nasal mucin and nasal tissue. A modified Boyden chamber was used to study eosinophil migration from both patients and healthy control subjects in the presence

of both extracts. RESULTS: Patients with chronic rhinosinusitis and all healthy control subjects demonstrated a concentration-dependent increased migration of eosinophils in the presence of both nasal mucin and nasal tissue extracts. The percentage of migration was consistently higher for eosinophils from patients with chronic rhinosinusitis compared with control subjects. The difference attained statistical significance in the presence of 50% tissue extract (median percentage of migration, 23.3% vs. 7.8% [P=.033]). CONCLUSIONS: Nasal mucin and nasal tissue in chronic rhinosinusitis contains chemoattractants, which can induce active eosinophil migration. The eosinophil migration from patients with chronic rhinosinusitis was consistently higher compared with eosinophils from healthy control subjects. Because the eosinophils were obtained from the peripheral blood, this finding suggests activation of eosinophils in the systemic circulation in chronic rhinosinusitis.

L109 ANSWER 11 OF 17 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 2002689073 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12447230
TITLE: Detection of fungal organisms in eosinophilic mucin using a fluorescein-labeled chitin-specific binding protein.
AUTHOR: Taylor Matthew J; **Ponikau Jens U**; **Sherris David A**; Kern Eugene B; Gaffey Thomas A; Kephart Gail; **Kita Hirohito**
CORPORATE SOURCE: Division of Allergy and Infection Diseases, Mayo Clinic, Rochester, MN 55905, USA.
CONTRACT NUMBER: AI 49245 (NIAID)
AI 50494-P3 (NIAID)
SOURCE: Otolaryngology--head and [redacted] surgery : offici[redacted]l of [redacted]y, Journal code: 8508176. ISSN: 0194-5998.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 14 Dec 2002
Last Updated on STN: 2 Jan 2003
Entered Medline: 31 Dec 2002
ED Entered STN: 14 Dec 2002
Last Updated on STN: 2 Jan 2003
Entered Medline: 31 Dec 2002
AB BACKGROUND: The ability to identify fungal hyphae in patients with chronic rhinosinusitis (CRS) has been inconsistent. A new fluorescein-labeled staining method targets chitin found in fungal cell walls. OBJECTIVE: We hypothesize that this method would be able to more consistently detect fungi within the mucin of CRS patients. METHODS: Fifty-four consecutive CRS surgical patients were evaluated. After ensuring sensitivity and specificity of this new method, all specimens were stained with either fluorescein-labeled chitinase or Grocott methanamine silver stain for comparison. RESULTS: All 54 specimens contained eosinophilic mucin on hematoxylin and eosin staining. One or more fungal hyphae could be visualized within the mucin of 54 (100%) of 54 specimens stained using the fluorescein-labeled chitinase. Only 41 (76%) of 54 of the specimens stained with the Grocott methanamine silver stain technique demonstrated fungi. CONCLUSION: The fluorescein-labeled chitinase-staining technique has greater sensitivity in detecting fungal organisms within eosinophilic mucin. Fungal organisms are present in the mucin of CRS patients.

L109 ANSWER 12 OF 17 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN

ACCESSION NUMBER: 2000-687377 [67] WPIX
DOC. NO. NON-CPI: N2000-508160
DOC. NO. CPI: C2000-209265
TITLE: Methods of diagnosing an eosinophil degranulating condition from a mucus sample using visual types of analysis or immunoassays.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): KERN, E; **KITA, H; PONIKAU, J; SHERRIS, D**
PATENT ASSIGNEE(S): (MAYO-N) MAYO FOUND MEDICAL EDUCATION & RES; (MAYO-N) MAYO FOUND MEDICAL EDUCATION RES
COUNTRY COUNT: 90
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000065341	A1	20001102	(200067)*	EN	56
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2000049748	A	20001110	(200109)		
US 6416955	B1	20020709	(200253)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000065341	A1	WO 2000-US10971	20000421
AU 2000049748	A	AU 2000-49748	20000421
US 6416955	B1 Provisional	US 1999-130603P	19990422
		US 2000-553790	20000421

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000049748	A Based on	WO 2000065341

PRIORITY APPLN. INFO: US 1999-130603P 19990422; US 2000-553790 20000421
ED 20001223
AN 2000-687377 [67] WPIX
AB WO 200065341 A UPAB: 20011129
NOVELTY - Method of diagnosing an eosinophil degranulating condition within mucus of a patient comprises determining whether the sample contains a horseshoe-shaped eosinophil granule structure, where presence of the structure indicates that the patient has an eosinophil degranulating condition.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method of diagnosing an eosinophil degranulating condition within a mucus sample from a patient comprising determining whether the sample contains a tissue-damaging amount of eosinophil granule content that is outside the granule;

(2) diagnostic kits comprising an antibody having specificity for a molecule from an eosinophil granule, and either a mucolytic agent or a mucus collector; and

(3) kits comprising a mucus collector and fixative for determination of whether a patient has an eosinophil degranulating condition within mucus.

USE - Conditions which can be diagnosed include a non invasive fungus-induced mucositis condition, e.g. rhinosinusitis, otitis media and bowel disease and asthma conditions (e.g. those responsive to antifungal treatment), and particularly chronic conditions. The patient is a human. Dwg.0/20

L109 ANSWER 13 OF 17 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2003197599 EMBASE
TITLE: Antifungal nasal washes for chronic rhinosinusitis: What's therapeutic - The wash or the antifungal? [6].
AUTHOR: Ferguson B.J.; **Ponikau J.U.**; **Sherris D.A.**; **Kita H.**; Kern E.B.
CORPORATE SOURCE: Dr. B.J. Ferguson, Department of Otolaryngology, School of Medicine, University of Pinsburgh, 200 Lothrop Street, Pittsburgh, PA 15213, United States
SOURCE: Journal of Allergy and Clinical Immunology, (1 May 2003) Vol. 111, No. 5, pp. 1137-1140. .
ISSN: 0091-6749 CODEN: JACIBY
COUNTRY: United States
DOCUMENT TYPE: Journal; Letter
FILE SEGMENT: 011 Otorhinolaryngology
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Jun 2003
Last Updated on STN: 5 Jun 2003
ED Entered STN: 5 Jun 2003
Last Updated on STN: 5 Jun 2003
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L109 ANSWER 14 OF 17 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:229308 BIOSIS
DOCUMENT NUMBER: PREV200400229824
TITLE: Treatment of chronic rhinosinusitis with intranasal amphotericin B: A prospective, randomized, placebo-controlled Trial.
AUTHOR(S): **Sherris, D. A.** [Reprint Author]; **Ponikau, J. U.**; Weaver, A.; Frigas, E.; **Kita, H.**
CORPORATE SOURCE: Otolaryngology, State University of New York at Buffalo, Buffalo, NY, USA
SOURCE: Journal of Allergy and Clinical Immunology, (February 2004) Vol. 113, No. 2 Supplement, pp. S331. print.
Meeting Info.: 60th Annual Meeting of the American Academy of Allergy, Asthma and Immunology (AAAAI). San Francisco, CA, USA. March 19-23, 2004. American Academy of Allergy, Asthma and Immunology.
CODEN: JACIBY. ISSN: 0091-6749.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Apr 2004
Last Updated on STN: 28 Apr 2004
ED Entered STN: 28 Apr 2004
Last Updated on STN: 28 Apr 2004

L109 ANSWER 15 OF 17 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on

STN
ACCESSION NUMBER: 2003:338217 BIOSIS
DOCUMENT NUMBER: PREV200300338217
TITLE: Extensive degranulation of **eosinophils** in the mucin, but not in the tissue, of chronic rhinosinusitis patients.
AUTHOR(S): **Ponikau, J. U.** [Reprint Author]; Kephart, G. M. [Reprint Author]; Kern, E. B. [Reprint Author]; **Sherris, D. A.** [Reprint Author]; **Kita, H.** [Reprint Author]
CORPORATE SOURCE: Mayo Clinic, Rochester, MN, USA
SOURCE: Journal of Allergy and Clinical Immunology, (February 2003) Vol. 111, No. 2 Abstract Supplement, pp. S125. print. Meeting Info.: AAAAI 60th Anniversary Meeting. Denver, CO, USA. March 07-12, 2003. American Academy of Allergy, Asthma and Immunology. CODEN: JACIBY. ISSN: 0091-6749.
DOCUMENT TYPE: Conference; (Meeting) Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Jul 2003 Last Updated on STN: 23 Jul 2003
ED Entered STN: 23 Jul 2003 Last Updated on STN: 23 Jul 2003

L109 ANSWER 16 OF 17 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:446996 BIOSIS
DOCUMENT NUMBER: PREV200200446996
TITLE: **Eosinophil** degranulating conditions.
AUTHOR(S): **Sherris, David** [Inventor, Reprint author]; Kern, Eugene [Inventor]; **Ponikau, Jens** [Inventor]; **Kita, Hirohito** [Inventor]
CORPORATE SOURCE: Rochester, MN, USA ASSIGNEE: Mayo Foundation for Medical Education and Research
PATENT INFORMATION: US 6416955 20020709
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (July 9, 2002) Vol. 1260, No. 2. http://www.uspto.gov/web/menu/patdata.html. e-file. CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Aug 2002 Last Updated on STN: 21 Aug 2002
ED Entered STN: 21 Aug 2002 Last Updated on STN: 21 Aug 2002
AB The invention provides methods and materials related to the diagnosis of **eosinophil** degranulating conditions. Specifically, the invention provides methods and materials that involve visual types of analysis (e.g., microscopic analysis) that are used to determine the presence or absence of a horseshoe-shaped **eosinophil** granule structure within a mucus sample collected from a mammal. The presence of a horseshoe-shaped **eosinophil** granule structure within a patient's mucus indicates that the patient has an **eosinophil** degranulating condition. In addition, the invention provides methods and materials that involve immunological types of analysis (e.g., immunoassays) that are used to determine if a patient's mucus contains a tissue-damaging amount of **eosinophil** granule content that is outside the **eosinophil** granule and within the mucus. Like the presence of a horseshoe-shaped

eosinophil granule structure, the presence of a tissue-damaging amount of **eosinophil** granule content outside the **eosinophil** granule and within the mucus indicates that the patient has an **eosinophil** degranulating condition. Further, the invention provides diagnostic kits that can be used to determine whether or not a patient has an **eosinophil** degranulating condition.

L109 ANSWER 17 OF 17 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:643419 SCISEARCH
THE GENUINE ARTICLE: 458DZ
TITLE: Extensive degranulation of **eosinophils** in the mucin of chronic rhinosinusitis patients
AUTHOR: **Ponikau J U (Reprint)**; **Sherris D A**; Kern E B; George T; **Kita H**
CORPORATE SOURCE: Mayo Clin & Mayo Fdn, Rochester, MN 55905 USA
COUNTRY OF AUTHOR: USA
SOURCE: CLINICAL AND EXPERIMENTAL ALLERGY, (JUL 2001) Vol. 31, No. 7, pp. 1153-1153. MA 24.
ISSN: 0954-7894.
PUBLISHER: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0
ENTRY DATE: Entered STN: 24 Aug 2001
Last Updated on STN: 24 Aug 2001
ED Entered STN: 24 Aug 2001
Last Updated on STN: 24 Aug 2001

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=> fil capl; d que l13
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FILE LAST UPDATED: 27 Sep 2006  (20060927/ED)

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L2         48797 SEA FILE=CAPLUS ABB=ON  SCREENING/CW
L4           139 SEA FILE=CAPLUS ABB=ON  ANTIGENS/CT(L)FUNG##/OBI
L5          1185 SEA FILE=CAPLUS ABB=ON  ALTERNARIA/CT
L6          5410 SEA FILE=CAPLUS ABB=ON  CANDIDA/CT
L7          7743 SEA FILE=CAPLUS ABB=ON  ASPERGILLUS/CT
L8           908 SEA FILE=CAPLUS ABB=ON  CLADOSPORIUM/CT
L11        10169 SEA FILE=CAPLUS ABB=ON  EOSINOPHIL+OLD/CT
L12       328218 SEA FILE=CAPLUS ABB=ON  DRUG#/CW
L13            8 SEA FILE=CAPLUS ABB=ON  (L2 OR L12) AND L11 AND (L4 OR L5 OR
                 L6 OR L7 OR L8)

=> s l13 not l1,l17
L110           7 L13 NOT (L1 OR L17)

=> fil medl
FILE 'MEDLINE' ENTERED AT 15:11:24 ON 28 SEP 2006

 FILE LAST UPDATED: 27 Sep 2006 (20060927/UP). FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 is now (26 Feb.) available.  For details
 on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.
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text search

printed w/ inventor search

Searched by Barb O'Bryen, STIC 2-2518

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> d que l32; d que l36; d que l38; d que l40
L22        15753 SEA FILE=MEDLINE ABB=ON  EOSINOPHILS/CT
L23          930 SEA FILE=MEDLINE ABB=ON  ALTERNARIA/CT
L24        24899 SEA FILE=MEDLINE ABB=ON  CANDIDA+NT/CT
L25        17352 SEA FILE=MEDLINE ABB=ON  ASPERGILLUS+NT/CT
L26          779 SEA FILE=MEDLINE ABB=ON  CLADOSPORIUM/CT
L27        94158 SEA FILE=MEDLINE ABB=ON  DRUG EVALUATION, PRECLINICAL+NT/CT
L30         4570 SEA FILE=MEDLINE ABB=ON  ANTIGENS, FUNGAL+NT/CT
L32            0 SEA FILE=MEDLINE ABB=ON  L22 AND L27 AND (L23 OR L24 OR L25 OR
                  L26 OR L30)


L22        15753 SEA FILE=MEDLINE ABB=ON  EOSINOPHILS/CT
L27        94158 SEA FILE=MEDLINE ABB=ON  DRUG EVALUATION, PRECLINICAL+NT/CT
L33         2219 SEA FILE=MEDLINE ABB=ON  L22(L)DE/CT - DE = drug effects
L35         1509 SEA FILE=MEDLINE ABB=ON  L22(L)CY/CT - CY = cytology
L36            3 SEA FILE=MEDLINE ABB=ON  L33 AND L35 AND L27


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L27        94158 SEA FILE=MEDLINE ABB=ON  DRUG EVALUATION, PRECLINICAL+NT/CT
L37       337882 SEA FILE=MEDLINE ABB=ON  IN VITRO/CT
L38            4 SEA FILE=MEDLINE ABB=ON  L22 AND L27 AND L37


L22        15753 SEA FILE=MEDLINE ABB=ON  EOSINOPHILS/CT
L27        94158 SEA FILE=MEDLINE ABB=ON  DRUG EVALUATION, PRECLINICAL+NT/CT
L39       799287 SEA FILE=MEDLINE ABB=ON  CELLS, CULTURED+NT/CT
L40            5 SEA FILE=MEDLINE ABB=ON  L39 AND L22 AND L27


=> s l36,l38,l40 not l21

L111           9 (L36 OR L38 OR L40) NOT L21  previously printed

=> fil embase; d que l56; d que l61; d que l65

FILE 'EMBASE' ENTERED AT 15:12:54 ON 28 SEP 2006
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 FILE COVERS 1974 TO 28 Sep 2006 (20060928/ED)

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 and biweekly.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.
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L47         1358 SEA FILE=EMBASE ABB=ON  FUNGUS ANTIGEN/CT
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L49        29141 SEA FILE=EMBASE ABB=ON  CANDIDA+NT/CT
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L51        17660 SEA FILE=EMBASE ABB=ON  ASPERGILLUS+NT/CT
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L54            3 SEA FILE=EMBASE ABB=ON  ASPERGILLUS ANTIGEN/CT
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                 L50 OR L51 OR L52 OR L53 OR L54)


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L46        74633 SEA FILE=EMBASE ABB=ON  DRUG SCREENING/CT
L60       592822 SEA FILE=EMBASE ABB=ON  IN VITRO STUDY/CT
L61            8 SEA FILE=EMBASE ABB=ON  L45 AND L46 AND L60


L45        13763 SEA FILE=EMBASE ABB=ON  EOSINOPHIL/CT
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L63        25386 SEA FILE=EMBASE ABB=ON  CELL VIABILITY/CT
L64       273163 SEA FILE=EMBASE ABB=ON  CELL CULTURE+NT/CT
L65            3 SEA FILE=EMBASE ABB=ON  L45 AND L46 AND (L62 OR L63 OR L64)


=> s l61,l65 not l55

L112          11 (L61 OR L65) NOT L55
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previously printed

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=> fil wpix; d que l81; d que l87

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FILE LAST UPDATED:          27 SEP 2006      <20060927/UP>
MOST RECENT DERWENT UPDATE:     200662        <200662/DW>
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http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<
'BI ABEX' IS DEFAULT SEARCH FIELD FOR 'WPIX' FILE
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L70        2449 SEA FILE=WPIX ABB=ON  B04-B02B2/MC OR B14-A04A/MC OR B04-F09A/M
                C OR B14-A04B/MC = Fungi or Aspergillus or candida
L71        1446 SEA FILE=WPIX ABB=ON  C04-B02B2/MC OR C14-A04A/MC OR C04-F09A/M
                C OR C14-A04B/MC = Fungi or Aspergillus or Candida
L72       14625 SEA FILE=WPIX ABB=ON  ALTERNARIA/BI,ABEX OR CANDIDA/BI,ABEX OR
                ASPERGILLUS/BI,ABEX OR CLADOSPORI?/BI,ABEX
L73         199 SEA FILE=WPIX ABB=ON  FUNG##/BI,ABEX(2A)ANTIGEN#/BI,ABEX
L74        4445 SEA FILE=WPIX ABB=ON  B04-B04C1/MC OR C04-B04C1/MC = Microbial antigen
L75        6417 SEA FILE=WPIX ABB=ON  DRUG#/BI,ABEX(2A)(SCREEN?/BI,ABEX OR
                DISCOVER?/BI,ABEX OR EVALUAT?/BI,ABEX)
L76        5060 SEA FILE=WPIX ABB=ON  B12-K04E1/MC OR C12-K04E1/MC = Drug disconary process
L80        1087 SEA FILE=WPIX ABB=ON  EOSINOPHIL#/BI,ABEX
L81           2 SEA FILE=WPIX ABB=ON  L80 AND (L70 OR L71 OR L72 OR L73 OR
                L74) AND (L75 OR L76)



L75        6417 SEA FILE=WPIX ABB=ON  DRUG#/BI,ABEX(2A)(SCREEN?/BI,ABEX OR
                DISCOVER?/BI,ABEX OR EVALUAT?/BI,ABEX)
L76        5060 SEA FILE=WPIX ABB=ON  B12-K04E1/MC OR C12-K04E1/MC
L77      112165 SEA FILE=WPIX ABB=ON  CULTUR?/BI,ABEX
L78       28520 SEA FILE=WPIX ABB=ON  VITRO/BI,ABEX
L79       39006 SEA FILE=WPIX ABB=ON  D05-H08/MC
L80        1087 SEA FILE=WPIX ABB=ON  EOSINOPHIL#/BI,ABEX
L86          18 SEA FILE=WPIX ABB=ON  (L75 OR L76) AND L80 AND (L77 OR L78 OR
                L79)
L87           1 SEA FILE=WPIX ABB=ON  L86 AND DEGRANULAT?/BI,ABEX


=> s l81,l87 not l69

L113          3 (L81 OR L87) NOT L69   previously printed

=> fil DRUGU, JICST-EPLUS, PASCAL, BIOTECHNO, BIOSIS, ESBIOBASE, BIOTECHDS,
CONFSCI, DISSABS, SCISEARCH

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=> d que l96; d que l107

L91       85103 SEA EOSINOPHIL#
L92      115320 SEA (DRUG# OR COMPOUND#)(2A)(SCREEN? OR EVALUAT? OR DISCOVER?)

L93        1652 SEA FUNG##(2A) ANTIGEN#
L94      281222 SEA ALTERNARIA OR CANDIDA OR ASPERGILLUS OR CLADOSPORI?
L96           0 SEA L91 AND L92 AND (L93 OR L94)



L91       85103 SEA EOSINOPHIL#
L92      115320 SEA (DRUG# OR COMPOUND#)(2A)(SCREEN? OR EVALUAT? OR DISCOVER?)

L97     2596477 SEA VITRO
L98     2951687 SEA CULTUR?
L99          61 SEA L91 AND L92 AND (L97 OR L98)
L100      26327 SEA DEGRANULAT?
L101       3600 SEA MAJOR BASIC
L102      55262 SEA NEUROTOXIN#
L103       9491 SEA CATIONIC PROTEIN#
L104     218360 SEA PEROXIDASE# OR PER OXIDASE#
L105     619518 SEA CYTOKINE#
L106     628138 SEA INTERLEUKIN# OR IL5 OR IL8 OR IL13 OR (IL(W)(5 OR 8 OR
                13))
L107         16 SEA L99 AND (L100 OR L101 OR L102 OR L103 OR L104 OR L105 OR
                L106)


=> s l107 not l95

L114         16 L107 NOT L95

=> => dup rem l110,l111,l113,l112,l114
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FILE 'BIOTECHNO' ENTERED AT 15:13:36 ON 28 SEP 2006

FILE 'BIOSIS' ENTERED AT 15:13:36 ON 28 SEP 2006

FILE 'ESBIOBASE' ENTERED AT 15:13:36 ON 28 SEP 2006

FILE 'BIOTECHDS' ENTERED AT 15:13:36 ON 28 SEP 2006

FILE 'SCISEARCH' ENTERED AT 15:13:36 ON 28 SEP 2006

PROCESSING COMPLETED FOR L110
PROCESSING COMPLETED FOR L111
PROCESSING COMPLETED FOR L113
PROCESSING COMPLETED FOR L112
PROCESSING COMPLETED FOR L114
L115 42 DUP REM L110 L111 L113 L112 L114 (4 DUPLICATES REMOVED)
ANSWERS '1-7' FROM FILE CAPLUS
ANSWERS '8-16' FROM FILE MEDLINE
ANSWERS '17-19' FROM FILE WPIX
ANSWERS '20-30' FROM FILE EMBASE
ANSWER '31' FROM FILE DRUGU
ANSWER '32' FROM FILE PASCAL
ANSWERS '33-42' FROM FILE BIOTECHDS

=> d ibib ed abs hitind 1-7; d iall 8-16; d iall abeq tech 17-19; d iall 20-42; fil hom

L115 ANSWER 1 OF 42 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:961475 CAPLUS
DOCUMENT NUMBER: 143:227950
TITLE: Cytokine inhibition of eosinophils
INVENTOR(S): Rothenberg, Marc Elliot; Fulkerson, Patricia Chandhok
PATENT ASSIGNEE(S): Children's Hospital Medical Center, USA
SOURCE: U.S. Pat. Appl. Publ., 33 pp., Cont.-in-part of U.S. Ser. No. 752,659.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005191273	A1	20050901	US 2005-91288	20050328
US 2004141951	A1	20040722	US 2004-752659	20040107
AU 2004204719	A1	20040729	AU 2004-204719	20040107
CA 2512090	AA	20040729	CA 2004-2512090	20040107
EP 1581166	A2	20051005	EP 2004-700562	20040107
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

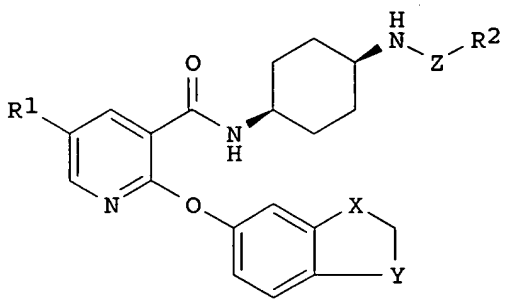
BR 2004006600	A	20051206	BR 2004-6600		20040107
JP 2006515619	T2	20060601	JP 2006-500801		20040107
CN 1829527	A	20060906	CN 2004-80006154		20040107
PRIORITY APPLN. INFO.:			US 2003-438412P	P	20030107
			US 2004-752659	A2	20040107
			WO 2004-US199	W	20040107

ED Entered STN: 02 Sep 2005
AB The cytokine CXCL9 (MIG) inhibited eosinophil responses by a CCR3- and Rac2-dependent mechanism.
IC ICM A61K038-19
INCL 424085100
CC 15-5 (Immunochemistry)
Section cross-reference(s): 1
IT **Aspergillus**
Asthma
Chemotaxis
Eosinophil
Human
Leukocyte
Lung
Neutrophil
Polymorphonuclear leukocyte
(cytokine inhibition of eosinophils)
IT **Drug** delivery systems
(injections, i.v.; cytokine inhibition of eosinophils)

L115 ANSWER 2 OF 42 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:78243 CAPLUS
DOCUMENT NUMBER: 142:155827
TITLE: Preparation of N-(cis-4-aminocyclohexyl)-2-(benzothienyloxy)nicotinamide derivatives as inhibitors of 3',5'-cyclic nucleotide phosphodiesterase 4 (PDE4)
INVENTOR(S): Smith, Mya Coral Helen; Watson, Christine Anne Louise
PATENT ASSIGNEE(S): Pfizer Inc, UK
SOURCE: U.S. Pat. Appl. Publ., 23 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005020639	A1	20050127	US 2004-896112	20040720
CA 2536383	AA	20050203	CA 2004-2536383	20040713
WO 2005009438	A1	20050203	WO 2004-IB2370	20040713
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1653958	A1	20060510	EP 2004-744029	20040713
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK
PRIORITY APPLN. INFO.: GB 2003-17471 A 20030725
US 2003-497088P P 20030822
WO 2004-IB2370 W 20040713
OTHER SOURCE(S): CASREACT 142:155827; MARPAT 142:155827
ED Entered STN: 28 Jan 2005
GI



I

AB This invention relates to nicotinamide derivs. of general formula (I) [R1 = H, halo, C1-4 alkyl; X = CH2, Y = S; or X = S and Y = CH2; Z = CO, SO2; R2 = each (un)substituted Ph, benzyl, naphthyl, heteroaryl or C3-8 cycloalkyl] or pharmaceutically acceptable salts or solvates thereof. These compds. are inhibitors of 3',5'-cyclic nucleotide phosphodiesterases (PDEs), i.e., PDE4A, PDE4B, PDE4C, and PDE4D which are isoforms or subtypes of the PDE4 isoenzyme family. They are particularly useful for the treatment of a great number of inflammatory, respiratory, and allergic diseases, disorders or conditions and for wounds and some of them are in clin. development mainly for treatment of asthma, chronic obstructive lung disease (COPD), bronchitis, and emphysema. Thus, cis-N-(4-aminocyclohexyl)-2-(2,3-dihydrobenzo[b]thiophen-6-yloxy)-5-fluoronicotinamide (150 mg, 0.39 mmol), imidazo[1,2-a]pyridine-8-carboxylic acid (87 mg, 0.43 mmol), 1-hydroxybenzotriazole hydrate (58 mg, 0.43 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (82 mg, 0.43 mmol) and 4-methylmorpholine (47 μL, 0.43 mmol) were dissolved in CH2Cl2 (20 mL) and the reaction mixture was stirred at room temperature for 18 h and was concentrated in vacuo. The residue was dissolved in DMF (10 mL) and stirred at room temperature for 18 h to give, after workup and silica gel chromatog., 130 mg (63%) imidazo[1,2-a]pyridine-8-carboxylic acid [cis-4-[[[2-[(2,3-dihydrobenzo[b]thiophen-6-yl)oxy]-5-fluoropyridin-3-yl]carbonyl]amino]-cyclohexyl]amide (II). Antiinflammatory properties of the nicotinamide derivs. I were demonstrated by their ability to inhibit TNFα release from human peripheral blood mononuclear cells. II showed IC50 of 0.6 nM in the above assay.

IC ICM C07D049-02
INCL 514338000; 546281100
CC 27-16 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 7, 28
IT **Aspergillus**
(aspergilloma; preparation of N-(cis-aminocyclohexyl)(benzothienyloxy)nicotinamide derivs. as inhibitors of 3',5'-cyclic nucleotide phosphodiesterase 4 (PDE4))
IT **Eosinophil**
(eosinophil-related disorder; preparation of N-(cis-aminocyclohexyl)(benzothienyloxy)nicotinamide derivs. as inhibitors of

3',5'-cyclic nucleotide phosphodiesterase 4 (PDE4))

IT Addison's disease
Allergy
Allergy inhibitors
Alzheimer's disease
Anti-AIDS agents
Anti-Alzheimer's agents
Anti-infective agents
Anti-inflammatory agents
Antiarthritics
Antiasthmatics
Antidepressants
Antidiabetic agents
Antiparkinsonian agents
Antiviral agents
Arthritis
Asbestosis
Asthma
Autoimmune disease
Bronchodilators
Cachexia
Central nervous system, disease
Chronic lymphocytic leukemia
Combination chemotherapy
Cystic fibrosis
Cytomegalovirus
Dermatitis
Dermatomyositis
Digestive tract, disease
Drug dependence
Emphysema
Eosinophilia
Graves' disease
Hay fever
Human herpesvirus
Human immunodeficiency virus 1
Human immunodeficiency virus 2
Human immunodeficiency virus 3
Infection
Inflammation
Influenza
Kidney, disease
Learning disorders
Lupus erythematosus
Multiple sclerosis
Myasthenia gravis
Nervous system agents
Osteoarthritis
Osteoporosis
Parkinson's disease
Pneumoconiosis
Prostate gland, disease
Psoriasis
Respiratory system, disease
Rheumatoid arthritis
Sarcoidosis
Silicosis
Ureter, disease
Urticaria
(preparation of N-(cis-aminocyclohexyl)(benzothienyloxy)nicotinamide derivs.

as inhibitors of 3',5'-cyclic nucleotide phosphodiesterase 4 (PDE4))

L115 ANSWER 3 OF 42 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:695788 CAPLUS
DOCUMENT NUMBER: 137:226941
TITLE: Use of certain steroids for treatment of a number of conditions including blood cell deficiencies
INVENTOR(S): Ahlem, Clarence N.; Reading, Christopher; Frincke, James; Stickney, Dwight; Lardy, Henry; Marwah, Padma; Marwah, Ashok; Prendergast, Patrick T.
PATENT ASSIGNEE(S): Hollis-Eden Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 383 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002069977	A1	20020912	WO 2002-US6708		20020301
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2003060425	A1	20030327	US 2001-820483		20010329
CA 2439687	AA	20020912	CA 2002-2439687		20020301
EP 1372664	A1	20040102	EP 2002-709780		20020301
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
ZA 2003006638	A	20040826	ZA 2003-6638		20020301
JP 2004537506	T2	20041216	JP 2002-569152		20020301
PRIORITY APPLN. INFO.:			US 2001-272624P	P	20010301
			US 2001-820483	A	20010329
			US 2001-323016P	P	20010910
			US 2001-328738P	P	20011011
			US 2001-340054P	P	20011101
			US 2001-338015P	P	20011108
			US 2001-343523P	P	20011220
			US 1998-109923P	P	19981124
			US 1998-109924P	P	19981124
			US 1998-110127P	P	19981127
			US 1998-112206P	P	19981215
			US 1999-124087P	P	19990311
			US 1999-126056P	P	19990323
			US 1999-137745P	P	19990603
			US 1999-140028P	P	19990616
			US 1999-145823P	P	19990727
			US 1999-414905	B2	19991008
			US 1999-161453P	P	19991025
			US 1999-449004	B2	19991124
			US 1999-449042	B2	19991124
			US 1999-449184	B2	19991124
			US 1999-461026	B2	19991215
			US 2000-535675	A2	20000323

US 2000-586672	B2	20000601
US 2000-586673	B2	20000601
US 2000-675470	A2	20000928
US 2000-257071P	P	20001220
WO 2002-US6708	W	20020301

OTHER SOURCE(S): MARPAT 137:226941
ED Entered STN: 13 Sep 2002
AB The invention relates to the use of compds. to treat a number of conditions, such as thrombocytopenia, neutropenia or the delayed effects of radiation therapy. Compds. that can be used in the invention include methyl-2,3,4-trihydroxy-1-O-(7,17-dioxoandrost-5-ene-3β-yl)-β-D-glucopyranosid ronate. Formulations containing the steroids are also exemplified.
IC ICM A61K031-565
ICS C07J001-00; A61P007-00
CC 2-4 (Mammalian Hormones)
Section cross-reference(s): 8, 32, 63
IT **Aspergillus**
Bacillus anthracis
Coccidioides immitis
Ebola virus
Escherichia coli
Eubacteria
Lassa virus
Mucor
Orthopoxvirus
Pseudomonas aeruginosa
Salmonella typhi
Variola virus
Vibrio cholerae
Yersinia pestis
(antiinfective activity; synthetic preparation and use of certain steroids for treatment of a number of conditions including blood cell deficiencies)
IT **Drug** delivery systems
(buccal; synthetic preparation and use of certain steroids for treatment of a number of conditions including blood cell deficiencies)
IT **Drug** delivery systems
(caplet; synthetic preparation and use of certain steroids for treatment of a number of conditions including blood cell deficiencies)
IT **Drug** delivery systems
(cyclodextrin formulation containing 16α-bromoepiandrosterone; synthetic preparation and use of certain steroids for treatment of a number of
conditions including blood cell deficiencies)
IT **Drug** delivery systems
(liposomes; synthetic preparation and use of certain steroids for treatment of a number of conditions including blood cell deficiencies)
IT **Drug** delivery systems
(parenterals; synthetic preparation and use of certain steroids for treatment of a number of conditions including blood cell deficiencies)
IT **Drug** delivery systems
(solns., containing 16α-bromoepiandrosterone; synthetic preparation and use of certain steroids for treatment of a number of conditions including blood cell deficiencies)
IT **Drug** delivery systems
(sublingual; synthetic preparation and use of certain steroids for treatment of a number of conditions including blood cell deficiencies)
IT **Drug** delivery systems
(suppositories, containing 16α-bromoepiandrosterone; synthetic preparation and use of certain steroids for treatment of a number of conditions

including blood cell deficiencies)

IT **Drug** delivery systems
(suspensions; synthetic preparation and use of certain steroids for treatment of a number of conditions including blood cell deficiencies)

IT Allergy
Allergy inhibitors
Alzheimer's disease
Analgesics
Aneurysm
Anti-AIDS agents
Anti-Alzheimer's agents
Anti-infective agents
Anti-inflammatory agents
Anti-ischemic agents
Antiarthritics
Antiasthmatics
Antibacterial agents
Anticholesteremic agents
Anticonvulsants
Antidepressants
Antidiabetic agents
Antimalarials
Antimigraine agents
Antiobesity agents
Antiparkinsonian agents
Antirheumatic agents
Antitumor agents
Antiviral agents
Antiviral agents
Arteriosclerosis
Atherosclerosis
Autoimmune disease
Basophil
Cardiovascular agents
Cardiovascular system, disease
Cognition enhancers
Eosinophil
Epilepsy
Erythrocyte
Fungicides
Hematopoietic precursor cell
Hepatitis C virus
Human
Human immunodeficiency virus 1
Hypercholesterolemia
Hypertension
Hypertriglyceridemia
Hypolipemic agents
Immunosuppression
Infection
Inflammation
Insomnia
Ischemia
Learning
Leukocyte
Lung, neoplasm
Malaria
Mammary gland, neoplasm
Memory, biological
Memory disorders

Metabolic disorders
Monocyte
Multiple sclerosis
Myelodysplastic syndromes
Neoplasm
Nervous system, disease
Nervous system agents
Neutrophil
Obesity
Osteoarthritis
Parasitemia
Parkinson's disease
Platelet (blood)
Prostate gland, neoplasm
Psoriasis
Rheumatoid arthritis
Schizophrenia
Skin, disease
Thrombosis
(synthetic preparation and use of certain steroids for treatment of a number of conditions including blood cell deficiencies)

IT **Drug** delivery systems
(tablets; synthetic preparation and use of certain steroids for treatment of a number of conditions including blood cell deficiencies)

IT **Drug** delivery systems
(transmucosal; synthetic preparation and use of certain steroids for treatment of a number of conditions including blood cell deficiencies)

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L115 ANSWER 4 OF 42 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:84648 CAPLUS
DOCUMENT NUMBER: 132:141941
TITLE: Conjugates and fusion proteins for treating secondary tissue damage and other inflammatory conditions and disorders
INVENTOR(S): Mcdonald, John R.; Coggins, Philip J.
PATENT ASSIGNEE(S): Osprey Pharmaceuticals Limited, Can.
SOURCE: PCT Int. Appl., 204 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000004926	A2	20000203	WO 1999-CA659	19990721
WO 2000004926	A3	20001102		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2335105	AA	20000203	CA 1999-2335105	19990721
AU 9948918	A1	20000214	AU 1999-48918	19990721

EP 1098664	A2	20010516	EP 1999-932572	19990721
EP 1098664	B1	20030806		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002521019	T2	20020716	JP 2000-560919	19990721
AT 246517	E	20030815	AT 1999-932572	19990721
EP 1346731	A1	20030924	EP 2003-76150	19990721
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
ES 2205849	T3	20040501	ES 1999-932572	19990721
US 2002168370	A1	20021114	US 2001-792793	20010222
HK 1037133	A1	20031107	HK 2001-107546	20011030
US 2003215421	A1	20031120	US 2003-375209	20030224
AU 2004202331	A1	20040624	AU 2004-202331	20040527
US 2006198820	A1	20060907	US 2006-361977	20060224
PRIORITY APPLN. INFO.:			US 1998-120523	A2 19980722
			US 1998-155186P	P 19980722
			AU 1999-48918	A3 19990721
			EP 1999-932572	A3 19990721
			WO 1999-CA659	W 19990721
			US 1999-360242	A3 19990722
			US 1999-453851	A3 19991202
			US 2001-792793	A1 20010222
			US 2003-375209	A1 20030224

ED Entered STN: 04 Feb 2000

AB Conjugates containing as a ligand a chemokine receptor-targeting agent, such as chemokines, and a targeted agent, such as a toxin are provided. These conjugates are used to treat inflammatory responses associated with activation, proliferation and migration of immune effector cells, including leukocyte cell types, neutrophils, macrophages, and eosinophils. The conjugates provided herein are used to lessen or inhibit these processes to prevent or at least lessen the resulting secondary effects. In particular, the conjugates are used to target toxins to receptors on secondary tissue damage-promoting cells. The ligand moiety can be selected to deliver the cell toxin to such secondary tissue damage-promoting cells as mononuclear phagocytes, leukocytes, natural killer cells, dendritic cells, and T and B lymphocytes, thereby suppressing the proliferation, migration, or physiol. activity of such cells. Among preferred conjugates are fusion proteins having a chemokine, or a biol. active fragment thereof, as the ligand moiety linked to a cell toxin via a peptide linker of from 2 to about 60 amino acid residues.

IC ICM A61K047-48

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 15

IT **Aspergillus**
(aspergillosis from; conjugates and fusion proteins for treating secondary tissue damage and other inflammatory conditions and disorders)

IT Alzheimer's disease
Anti-inflammatory agents
Antiarthritics
Antiparkinsonian agents
Antirheumatic agents
Antitumor agents
Atherosclerosis
B cell (lymphocyte)
Basophil
Behcet's syndrome
Bronchodilators
Cell migration

Cell proliferation
Coupling agents
Dendritic cell
Down's syndrome
Drug targeting
Encephalitis
Encephalomyelitis
Eosinophil
Genetic vectors
Granuloma
Heart, disease
Hodgkin's disease
Immunosuppressants
Inflammation
Molecular cloning
Multiple sclerosis
Neutrophil
Osteoarthritis
Parkinson's disease
Plasmid vectors
Pneumonia
Protein sequences
Sarcoidosis
T cell (lymphocyte)
Venoms
cDNA library
cDNA sequences
(conjugates and fusion proteins for treating secondary tissue damage and other inflammatory conditions and disorders)

IT **Drug** delivery systems
(injections, i.m.; conjugates and fusion proteins for treating secondary tissue damage and other inflammatory conditions and disorders)

IT **Drug** delivery systems
(injections, i.p.; conjugates and fusion proteins for treating secondary tissue damage and other inflammatory conditions and disorders)

IT **Drug** delivery systems
(injections, i.v.; conjugates and fusion proteins for treating secondary tissue damage and other inflammatory conditions and disorders)

IT **Drug** delivery systems
(injections, intraarticular; conjugates and fusion proteins for treating secondary tissue damage and other inflammatory conditions and disorders)

IT **Drug** delivery systems
(injections, intracisternal; conjugates and fusion proteins for treating secondary tissue damage and other inflammatory conditions and disorders)

IT **Drug** delivery systems
(injections, intradermal; conjugates and fusion proteins for treating secondary tissue damage and other inflammatory conditions and disorders)

IT **Drug** delivery systems
(injections, intraventricular; conjugates and fusion proteins for treating secondary tissue damage and other inflammatory conditions and disorders)

IT **Drug** delivery systems
(intratracheal; conjugates and fusion proteins for treating secondary tissue damage and other inflammatory conditions and disorders)

IT **Drug** delivery systems
(local; conjugates and fusion proteins for treating secondary tissue damage and other inflammatory conditions and disorders)
IT **Drug** delivery systems
(ophthalmic; conjugates and fusion proteins for treating secondary tissue damage and other inflammatory conditions and disorders)
IT **Drug** delivery systems
(targeted; conjugates and fusion proteins for treating secondary tissue damage and other inflammatory conditions and disorders)
IT **Drug** delivery systems
(topical; conjugates and fusion proteins for treating secondary tissue damage and other inflammatory conditions and disorders)

L115 ANSWER 5 OF 42 CAPLUS COPY [redacted] OR SIN
ACCESSION NUMBER: 1999:202082 CAPLUS
DOCUMENT NUMBER: 130:306586
TITLE: Methods and materials for treating and preventing inflammation of mucosal tissue using antifungal agents, and diagnostic methods and materials
INVENTOR(S): Ponikau, Jens
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9920261	A2	19990429	WO 1998-US22403	19981022
WO 9920261	A3	20000217		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
ZA 9809650	A	19990423	ZA 1998-9650	19981022
CA 2308201	AA	19990429	CA 1998-2308201	19981022
AU 9911959	A1	19990510	AU 1999-11959	19981022
EP 1024814	A2	20000809	EP 1998-955065	19981022
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200001117	T2	20000921	TR 2000-200001117	19981022
US 6207703	B1	20010327	US 1998-176990	19981022
US 2001002400	A1	20010531	US 1998-177273	19981022
US 6291500	B2	20010918		
EE 200000253	A	20010615	EE 2000-253	19981022
US 2001006944	A1	20010705	US 1998-177164	19981022
BR 9814615	A	20011016	BR 1998-14615	19981022
JP 2001520188	T2	20011030	JP 2000-516659	19981022
US 2002052390	A1	20020502	US 1998-177659	19981022
TW 236905	B1	20050801	TW 1998-87117691	19981026
US 2003091510	A1	20030515	US 2000-500115	20000208
NO 2000002069	A	20000621	NO 2000-2069	20000419
BG 104371	A	20001229	BG 2000-104371	20000424
US 2001031779	A1	20011018	US 2001-865785	20010525

US 6555566	B2	20030429		
US 2003153516	A1	20030814	US 2002-293924	20021113
US 2005124561	A1	20050609	US 2004-962196	20041008
AU 2005202469	A1	20050623	AU 2005-202469	20050607
JP 2006096770	A2	20060413	JP 2005-375253	20051227
PRIORITY APPLN. INFO.:			US 1997-62709P	P 19971022
			US 1997-63414P	P 19971028
			US 1997-63418P	P 19971028
			US 1998-83272P	P 19980428
			US 1998-86397P	P 19980522
			JP 2000-516659	A3 19981022
			US 1998-177164	B1 19981022
			US 1998-177273	A1 19981022
			WO 1998-US22403	W 19981022
			US 2000-500115	A1 20000208
			US 2001-865785	A1 20010525
			AU 2002-300886	A3 20020905

ED Entered STN: 07 May 1999

AB The invention involves methods and materials for treating and preventing non-invasive fungus-induced mucositis. Specifically, the invention involves administering an antifungal agent such that it contacts mucus in an amount, at a frequency, and for a duration effective to prevent, reduce, or eliminate non-invasive fungus-induced rhinosinusitis. This invention also provides methods and materials for diagnosing non-invasive fungus-induced rhinosinusitis and culturing non-invasive fungus from a mammalian mucus sample as well as specific antifungal formulations and medical devices for treating and preventing non-invasive fungus-induced rhinosinusitis. In addition, the invention provides methods and materials for treating and preventing other non-invasive fungus-induced mucositis conditions such as chronic otitis media, chronic colitis, and Crohn's disease. Further, the invention involves methods and materials for treating and preventing chronic asthma symptoms.

IC ICM A61K031-00

CC 1-7 (Pharmacology)
Section cross-reference(s): 63

IT Acremonium
Alternaria
Anti-inflammatory agents
Antiasthmatics
Arachniotus citrinus
Aspergillus
Aspergillus fumigatus
Aspergillus nidulans
Aureobasidium
Candida
Chrysosporium
Cladosporium
Cryptococcus (fungus)
Drug delivery systems
Eosinophilia
Epicoccum
Exophiala jeanselmei
Fungi
Fungicides
Fusarium
Geotrichum
Mucor
Oidiodendron
Paecilomyces lilacinus
Papularia

Penicillium
Phoma
Pithomyces
Rhodotorula
Scolecobasidium
Scopulariopsis
Trichoderma
Ustilago
Yeast
(antifungal agents for treating and preventing inflammation of mucosal tissue, and diagnostic methods and materials)

IT Antibacterial agents
Antibiotics
Decongestants
Drugs
Expectorants
Immunosuppressants
Vasoconstrictors
(antifungal agents for treating and preventing inflammation of mucosal tissue, diagnostic methods and materials, and use with other agents)

IT **Antigens**
RL: PUR (Purification or recovery); PREP (Preparation)
(**fungal**; antifungal agents for treating and preventing inflammation of mucosal tissue, and diagnostic methods and materials)

IT **Drug** delivery systems
(gels; antifungal agents for treating and preventing inflammation of mucosal tissue, and diagnostic methods and materials)

IT **Drug** delivery systems
(liqs.; antifungal agents for treating and preventing inflammation of mucosal tissue, and diagnostic methods and materials)

IT **Eosinophil**
(migration; antifungal agents for treating and preventing inflammation of mucosal tissue, and diagnostic methods and materials)

IT **Drug** delivery systems
(ointments, and Whitefield's ointment; antifungal agents for treating and preventing inflammation of mucosal tissue, and diagnostic methods and materials)

IT **Drug** delivery systems
(ointments, creams; antifungal agents for treating and preventing inflammation of mucosal tissue, and diagnostic methods and materials)

IT **Drug** delivery systems
(pastes; antifungal agents for treating and preventing inflammation of mucosal tissue, and diagnostic methods and materials)

IT **Drug** delivery systems
(powders; antifungal agents for treating and preventing inflammation of mucosal tissue, and diagnostic methods and materials)

IT **Drug** delivery systems
(solids; antifungal agents for treating and preventing inflammation of mucosal tissue, and diagnostic methods and materials)

IT **Drug** delivery systems
(solns.; antifungal agents for treating and preventing inflammation of mucosal tissue, and diagnostic methods and materials)

IT **Drug** delivery systems
(sprays; antifungal agents for treating and preventing inflammation of mucosal tissue, and diagnostic methods and materials)

IT **Drug** delivery systems
(suspensions; antifungal agents for treating and preventing inflammation of mucosal tissue, and diagnostic methods and materials)

IT **Drug** delivery systems
(tinctures; antifungal agents for treating and preventing inflammation

of mucosal tissue, and diagnostic methods and materials)

L115 ANSWER 6 OF 42 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:222963 CAPLUS
DOCUMENT NUMBER: 130:262121
TITLE: Peptide inhibitors of hematopoietins interleukin-3, interleukin-5 and granulocyte/macrophage colony stimulating factor and of Lyn kinase, and therapeutic uses thereof
INVENTOR(S): Alam, Rafeul; Adachi, Tetsuya
PATENT ASSIGNEE(S): Astra Aktiebolag, Swed.
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9915561	A1	19990401	WO 1998-SE1687		19980921
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
AU 9892890	A1	19990412	AU 1998-92890		19980921
PRIORITY APPLN. INFO.:			US 1997-59630P	P	19970923
			WO 1998-SE1687	W	19980921

ED Entered STN: 12 Apr 1999
AB Peptide inhibitors of the hematopoietins interleukin-3, interleukin-5 and granulocyte/macrophage colony-stimulating factor signaling are provided, wherein the peptides inhibit the activation of Lyn tyrosine kinase and thereby block signal transduction via the hematopoietin βc receptor common to interleukin-3, interleukin-5 and granulocyte/macrophage colony-stimulating factor. Also provided is a method of treating a condition involving increased production and function of eosinophils and other granulocytes, comprising the step of administering a pharmacol. ED of the pharmaceutical composition disclosed herein.
IC ICM C07K014-715
ICS A61K038-19; C12N009-12
CC 1-7 (Pharmacology)
Section cross-reference(s): 15, 63
IT **Aspergillus**
(aspergillosis from, allergic bronchopulmonary aspergillosis; peptide inhibitors of hematopoietins interleukin-3, interleukin-5 and granulocyte/macrophage colony stimulating factor and of Lyn kinase, and therapeutic use)
IT **Eosinophil**
(diseases, idiopathic eosinophilic syndrome and Loeffler's syndrome; peptide inhibitors of hematopoietins interleukin-3, interleukin-5 and granulocyte/macrophage colony stimulating factor and of Lyn kinase, and therapeutic use)
IT Antiasthmatics
B cell (lymphocyte)
Basophil
Bone marrow

Cell differentiation
Cytotoxic agents
Drug delivery systems
Eosinophil
Megakaryocyte
Myelocyte
Myelodysplastic syndromes
Polymorphonuclear leukocyte
Signal transduction, biological
T cell (lymphocyte)
(peptide inhibitors of hematopoietins interleukin-3, interleukin-5 and granulocyte/macrophage colony stimulating factor and of Lyn kinase, and therapeutic use)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

[redacted] COPYRIGHT 2006 [redacted]

ACCESSION NUMBER: 1998:71160 CAPLUS
DOCUMENT NUMBER: 128:153150
TITLE: Therapeutic multispecific compounds comprised of anti-Fcα receptor antibodies
INVENTOR(S): Deo, Yashwant M.; Graziano, Robert; Keler, Tibor
PATENT ASSIGNEE(S): Medarex, Inc., USA; Deo, Yashwant M.; Graziano, Robert; Keler, Tibor
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9802463	A1	19980122	WO 1997-US12013	19970710
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5922845	A	19990713	US 1996-678194	19960711
CA 2259371	AA	19980122	CA 1997-2259371	19970710
AU 9737233	A1	19980209	AU 1997-37233	19970710
AU 705643	B2	19990527		
EP 914346	A1	19990512	EP 1997-934094	19970710
EP 914346	B1	20060301		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1230198	A	19990929	CN 1997-197841	19970710
JP 2000505091	T2	20000425	JP 1998-506141	19970710
JP 3519415	B2	20040412		
RU 2201766	C2	20030410	RU 1999-103303	19970710
IL 128003	A1	20030624	IL 1997-128003	19970710
AT 318845	E	20060315	AT 1997-934094	19970710
US 6303755	B1	20011016	US 1999-262724	19990304
PRIORITY APPLN. INFO.:			US 1996-678194 A2	19960711
			WO 1997-US12013 W	19970710

ED Entered STN: 06 Feb 1998

AB Multispecific compds. comprising at least one binding determinant which binds to the Fcα receptor on an effector cell. The other binding determinant(s) binds(s) to one or more antigens on a target cell, e.g., the Neu/Her-2 proto-oncogene product or the epidermal growth factor receptor on cancer cells, or to Candida antigens on infected cells. Examples are biospecific and trispecific antibodies. Therapeutic use of said multispecific compds. for treatment of cancers or pathogen infections.

IC ICM C07K016-46
ICS A61K039-395; A61K038-19; A61K035-14; G01N033-68; C07K016-28; C07K016-32; C07K016-30; C07K014-33; C07K016-14; A61K039-395; A61K038-19

CC 15-3 (Immunochemistry)

IT Autoimmune disease
Bacteria (Eubacteria)
Basophil
Blood
Bone, neoplasm
Candida
Candida albicans
Drug design
Eosinophil
Fungi
Infection
Kidney, neoplasm
Leukocyte
Liver, neoplasm
Lung, neoplasm
Lymphocyte
Macrophage
Monocyte
Neoplasm
Neutrophil
Ovary, neoplasm
Pancreas, neoplasm
Pathogen
Protein sequences
Protozoa
Testis, neoplasm
Virus
cDNA sequences
(therapeutic multispecific compds. comprised of anti-Fcα receptor antibodies)

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L115 ANSWER 8 OF 42 MEDLINE on STN
ACCESSION NUMBER: 2005217844 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15792791
TITLE: Evaluating the prophylactic potential of the phtalimide derivative LASSBio 552 on allergen-evoked inflammation in rats.
AUTHOR: Neves Josiane S; Lima Lidia M; Fraga Carlos A M; Barreiro Eliezer J; Miranda Ana L P; Diaz Bruno L; Balduino Alex; Siqueira Rodrigo de Azeredo; e Silva Patricia M R; Martins Marco A
CORPORATE SOURCE: Departamento de Fisiologia e Farmacodinamica, Instituto

Oswaldo Cruz-FIOCRUZ, Av. Brasil 4365, Caixa Postal 926, Rio de Janeiro, Brazil.
SOURCE: European journal of pharmacology, (2005 Mar 28) Vol. 511, No. 2-3, pp. 219-27.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200507
ENTRY DATE: Entered STN: 28 Apr 2005
Last Updated on STN: 27 Jul 2005
Entered Medline: 26 Jul 2005

ABSTRACT:
A previous study showed that the novel tetrazolephtalimide derivative LASSBio 552 (2-4-[3-(1H-1,2,3,4-tetraazol-5-yl)propoxy]phenethyl-1,3-isoindolinedione) prevents LTD(4)-evoked tracheal contraction. This led us to examine the putative anti-inflammatory effect of LASSBio 552 in comparison with the leukotriene CysLT(1) receptor antagonist zafirlukast using a model of allergic pleurisy in rats. Treatment with either LASSBio 552 (24-96 micromol/kg, i.p.) or zafirlukast (9-72 micromol/kg, i.p.), 1 h before challenge, inhibited eosinophil and mononuclear cell influx into the pleural cavity 24 h post-challenge, but failed to alter the increased levels of eotaxin, plasma leakage, mast cell degranulation and neutrophil infiltration noted 6 h post-challenge. CD4(+) T cell recruitment 24 h post-challenge was also sensitive to LASSBio 552. This treatment failed to alter cysteinyl leukotriene production at 6 h, but clearly inhibited the phenomenon 24 h and 48 h post-challenge. In in vitro settings LASSBio 552 inhibited allergen-evoked cysteinyl leukotriene generation from isolated mast cells, while histamine release remained unchanged. It also slightly inhibited cysteinyl leukotriene production by eosinophils and mononuclear cells triggered by Ca(+2) ionophore A23187. A leukotriene CysLT(1) receptor transfected cell-based assay revealed that LASSBio 552 did not prevent LTD(4)-evoked Ca(+2) influx, indicating that it was not a leukotriene CysLT(1) receptor antagonist. These findings indicate that LASSBio 552 is able to inhibit eosinophil influx triggered by allergen chalenge in a mechanism at least partially associated with suppression of CD4(+) T cell influx and cysteinyl leukotriene production.

CONTROLLED TERM: Check Tags: Female; Male
*Allergens: IM, immunology
Animals
Anti-Asthmatic Agents: PD, pharmacology
CD4-Positive T-Lymphocytes: CY, cytology
CD4-Positive T-Lymphocytes: DE, drug effects
CHO Cells
Calcium: ME, metabolism
Cell Movement: DE, drug effects
Chemokines, CC: BI, biosynthesis
Comparative Study
Cricetinae
Cricetulus
Cysteine: ME, metabolism
Dose-Response Relationship, Drug
Drug Evaluation, Preclinical
Eosinophils: CY, cytology
Eosinophils: DE, drug effects
Indoles: CH, chemistry
*Indoles: PD, pharmacology
Inflammation: IM, immunology
*Inflammation: PC, prevention & control
Leukotriene D4: PD, pharmacology

Leukotrienes: ME, metabolism
Membrane Proteins: GE, genetics
Membrane Proteins: ME, metabolism
Pleura: DE, drug effects
Pleura: IM, immunology
Pleurisy: IM, immunology
Pleurisy: ME, metabolism
Pleurisy: PC, prevention & control
Rats
Rats, Wistar
Receptors, Leukotriene: GE, genetics
Receptors, Leukotriene: ME, metabolism
Research Support, Non-U.S. Gov't
Tetrazoles: CH, chemistry
*Tetrazoles: PD, pharmacology
Tosyl Compounds: PD, pharmacology
Transfection

CAS REGISTRY NO.: 107753-78-6 (zafirlukast); 52-90-4 (Cysteine); 73836-78-9 (Leukotriene D4); 7440-70-2 (Calcium)

CHEMICAL NAME: 0 (2-4-(3-(1H-1,2,3,4-tetraazol-5-yl)propoxy)phenethyl-1,3-isoindolinedione); 0 (Allergens); 0 (Anti-Asthmatic Agents); 0 (CCL11 chemokine); 0 (Chemokines, CC); 0 (Indoles); 0 (Leukotrienes); 0 (Membrane Proteins); 0 (Receptors, Leukotriene); 0 (Tetrazoles); 0 (Tosyl Compounds); 0 (cysteinyl-leukotriene); 0 (leukotriene D4 receptor)

L115 ANSWER 9 OF 42 MEDLINE on STN
ACCESSION NUMBER: 2001450281 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11496242
TITLE: Preclinical efficacy and safety of mepolizumab (SB-240563), a humanized monoclonal antibody to IL-5, in cynomolgus monkeys.
AUTHOR: Hart T K; Cook R M; Zia-Amirhosseini P; Minthorn E; Sellers T S; Maleeff B E; Eustis S; Schwartz L W; Tsui P; Appelbaum E R; Martin E C; Bugelski P J; Herzyk D J
CORPORATE SOURCE: Department of Safety Assessment, GlaxoSmithKline Pharmaceuticals, King of Prussia, PA 19406, USA.
SOURCE: The Journal of allergy and clinical immunology, (2001 Aug) Vol. 108, No. 2, pp. 250-7.
Journal code: 1275002. ISSN: 0091-6749.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 13 Aug 2001
Last Updated on STN: 10 Sep 2001
Entered Medline: 6 Sep 2001

ABSTRACT:
BACKGROUND: Allergic respiratory diseases are characterized by large numbers of eosinophils and their reactive products in airways and blood; these are believed to be involved in progressive airway damage and remodeling. IL-5 is the principal cytokine for eosinophil maturation, differentiation, and survival. Mepolizumab (SB-240563), a humanized monoclonal antibody (mAb) specific for human IL-5, is currently in clinical trials for treatment of asthma. OBJECTIVE: The purpose of this study was to characterize the pharmacologic activity and long-term safety profile of an anti--human IL-5 mAb to support clinical trials in asthmatic patients. METHODS: Naive and Ascaris suum -sensitive cynomolgus monkeys received various dose levels of mepolizumab

and were monitored for acute and chronic pharmacologic and toxic responses. RESULTS: To support preclinical safety assessment, cynomolgus monkey IL-5 was cloned, expressed, and characterized. Although monkey IL-5 differs from human IL-5 by 2 amino acids (Ala27Gly and Asn40His), mepolizumab has comparable inhibitory activity against both monkey IL-5 and human IL-5. In A suum--sensitive monkeys, single doses of mepolizumab significantly reduced blood eosinophilia, eosinophil migration into lung airways, and levels of RANTES and IL-6 in lungs for 6 weeks. However, mepolizumab did not affect acute bronchoconstrictive responses to inhaled A suum. In an IL-2--induced eosinophilia model (up to 50% blood eosinophilia), 0.5 mg/kg mepolizumab blocked eosinophilia by >80%. Single-dose and chronic (6 monthly doses) intravenous and subcutaneous toxicity studies in naive monkeys found no target organ toxicity or immunotoxicity up to 300 mg/kg. Monkeys did not generate anti-human IgG antibodies. Monthly mepolizumab doses greater than 5 mg/kg caused an 80% to 100% decrease in blood and bronchoalveolar lavage eosinophils lasting 2 months after dosing, and there was no effect on eosinophil precursors in bone marrow after 6 months of treatment. Eosinophil decreases correlated with mepolizumab plasma concentrations (half-life = 13 days). CONCLUSION: These studies demonstrate that chronic antagonism of IL-5 by mepolizumab in monkeys is safe and has the potential, through long-term reductions in circulating and tissue-resident eosinophils, to be beneficial therapy for chronic inflammatory respiratory diseases.

CONTROLLED TERM: Check Tags: Male
Animals
Anti-Asthmatic Agents: PD, pharmacology
*Anti-Asthmatic Agents: TU, therapeutic use
Anti-Asthmatic Agents: TO, toxicity
Antibodies, Monoclonal: PD, pharmacology
*Antibodies, Monoclonal: TU, therapeutic use
Antibodies, Monoclonal: TO, toxicity
*Asthma: TH, therapy
Cell Count
Cloning, Molecular
Drug Evaluation, Preclinical
Eosinophils: CY, cytology
***Eosinophils: DE, drug effects**
Immunotherapy
Interleukin-5: AI, antagonists & inhibitors
Interleukin-5: GE, genetics
*Interleukin-5: IM, immunology
Macaca fascicularis
Research Support, Non-U.S. Gov't
Safety
Species Specificity

CHEMICAL NAME: 0 (Anti-Asthmatic Agents); 0 (Antibodies, Monoclonal); 0 (Interleukin-5); 0 (mepolizumab)

L115 ANSWER 10 OF 42 MEDLINE on STN
ACCESSION NUMBER: 2000438389 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10966751
TITLE: Symmetrical bis(heteroarylmethoxyphenyl)alkylcarboxylic acids as inhibitors of leukotriene biosynthesis.
AUTHOR: Kolasa T; Gunn D E; Bhatia P; Basha A; Craig R A; Stewart A O; Bouska J B; Harris R R; Hulkower K I; Malo P E; Bell R L; Carter G W; Brooks C D
CORPORATE SOURCE: Immunoscience Research, Abbott Laboratories, D41K, R13-4, 1401 Sheridan Road, North Chicago, Illinois 60064, USA.
SOURCE: Journal of medicinal chemistry, (2000 Aug 24) Vol. 43, No. 17, pp. 3322-34.
Journal code: 9716531. ISSN: 0022-2623.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 28 Sep 2000
Last Updated on STN: 28 Sep 2000
Entered Medline: 21 Sep 2000

ABSTRACT:
Symmetrical bis(quinolylmethoxyphenyl)alkylcarboxylic acids were investigated as inhibitors of leukotriene biosynthesis and 4, 4-bis(4-(2-quinolylmethoxy)phenyl)pentanoic acid sodium salt (47.Na) met our design parameters for a drug candidate (ABT-080). This compound was readily synthesized in three steps from commercially available diphenolic acid. Against intact human neutrophils, 47.Na inhibited ionophore-stimulated LTB(4) formation with an IC(50) = 20 nM. In zymosan-stimulated mouse peritoneal macrophages producing both LTC(4) and PGE(2), 47.Na showed 9000-fold selectivity for inhibition of LTC(4) (IC(50) = 0.16 nM) over PGE(2) (IC(50) = 1500 nM). Preliminary pharmacokinetic evaluation in rat and cynomolgus monkey demonstrated good oral bioavailability and elimination half-lives of 9 and 5 h, respectively. Pharmacological evaluation of leukotriene inhibition with oral dosing was demonstrated in a rat pleural inflammation model (ED(50) = 3 mg/kg) and a rat peritoneal passive anaphylaxis model (LTB(4), ED(50) = 2.5 mg/kg; LTE(4), ED(50) = 1.0 mg/kg). In a model of airway constriction induced by antigen challenge in actively sensitized guinea pigs, 47.Na dosed orally blocked bronchoconstriction with an ED(50) = 0.4 mg/kg, the most potent activity we have observed for any leukotriene inhibitor in this model. The mode of inhibitory action of 47.Na occurs at the stage of 5-lipoxygenase biosynthesis as it blocks both leukotriene pathways leading to LTB(4) and LTC(4) but not PGH(2) biosynthesis. However, 47.Na does not inhibit 5-lipoxygenase catalysis in a broken cell enzyme assay; therefore it is likely that 47.Na acts as a FLAP inhibitor.

CONTROLLED TERM:
Administration, Oral
Anaphylaxis: ME, metabolism
Animals
Bronchoalveolar Lavage Fluid: CY, cytology
Bronchoconstriction: DE, drug effects
*Carboxylic Acids: CS, chemical synthesis
Carboxylic Acids: CH, chemistry
Carboxylic Acids: PK, pharmacokinetics
Carboxylic Acids: PD, pharmacology
Drug Evaluation, Preclinical
Eosinophils: PA, pathology
Guinea Pigs
Humans
In Vitro
*Leukotriene Antagonists: CS, chemical synthesis
Leukotriene Antagonists: CH, chemistry
Leukotriene Antagonists: PK, pharmacokinetics
Leukotriene Antagonists: PD, pharmacology
Leukotriene B4: AI, antagonists & inhibitors
Leukotriene B4: BI, biosynthesis
Lung: PA, pathology
Macaca fascicularis
Mice
Neutrophils: ME, metabolism
*Pentanoic Acids: CS, chemical synthesis
Pentanoic Acids: CH, chemistry
Pentanoic Acids: PK, pharmacokinetics
Pentanoic Acids: PD, pharmacology

Peritoneum: ME, metabolism
Pleurisy: CI, chemically induced
Pleurisy: DT, drug therapy
*Quinolines: CS, chemical synthesis
Quinolines: CH, chemistry
Quinolines: PK, pharmacokinetics
Quinolines: PD, pharmacology
Rats
Structure-Activity Relationship
CAS REGISTRY NO.: 71160-24-2 (Leukotriene B4)
CHEMICAL NAME: 0 (ABT 080); 0 (Carboxylic Acids); 0 (Leukotriene Antagonists); 0 (Pentanoic Acids); 0 (Quinolines)

L115 ANSWER 11 OF 42 MEDLINE on STN
ACCESSION NUMBER: 1998440460 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9767640
TITLE: Design, synthesis, and biological activities of new thieno[3,2-d] pyrimidines as selective type 4 phosphodiesterase inhibitors.
AUTHOR: Crespo M I; Pages L; Vega A; Segarra V; Lopez M; Domenech T; Miralpeix M; Beleta J; Ryder H; Palacios J M
CORPORATE SOURCE: Almirall Prodesfarma S.A., Research Center, Cardener 68-74, 08024 Barcelona, Spain.
SOURCE: Journal of medicinal chemistry, (1998 Oct 8) Vol. 41, No. 21, pp. 4021-35.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 6 Jan 1999
Last Updated on STN: 3 Mar 2000
Entered Medline: 3 Nov 1998

ABSTRACT:
A common pharmacophore for compounds structurally related to nitraquazone has been derived. Using this pharmacophore, new structures have been designed, synthesized, and evaluated for their inhibitory potencies against cyclic adenosine 5'-monophosphate (cAMP) specific phosphodiesterase (PDE 4). From these compounds, 4-benzylamino-2-butylthieno[3,2-d]pyrimidine (4) was selected for optimization. The effects of changes to the lipophilic groups and the amino linkage on the PDE 4 activity have been investigated. As a result, some potent PDE 4 inhibitors, selective with respect to PDE 3, have been identified. A selected group of compounds have been further evaluated for their ability to displace [3H]rolipram from its binding site and also to potentiate isoprenaline-induced cAMP accumulation in isolated guinea pig eosinophils. Of these, 2-butyl-4-cyclohexylaminothieno[3,2-d]pyrimidine (33) has an interesting profile, with an important improvement in PDE 4/[3H]rolipram ratio with respect to reference drugs, and good activity in cAMP potentiation, consistent with efficient cell penetration.

CONTROLLED TERM: Check Tags: Male
*3',5'-Cyclic-Nucleotide Phosphodiesterase: ME, metabolism
Animals
*Anti-Asthmatic Agents: CS, chemical synthesis
Anti-Asthmatic Agents: CH, chemistry
Anti-Asthmatic Agents: ME, metabolism
Anti-Asthmatic Agents: PD, pharmacology
Binding, Competitive
Cyclic AMP: ME, metabolism
*Drug Design

Drug Evaluation, Preclinical
Eosinophils: DE, drug effects
Eosinophils: ME, metabolism
Guinea Pigs
In Vitro
Models, Molecular
Myocardium: EN, enzymology
*Phosphodiesterase Inhibitors: CS, chemical synthesis
Phosphodiesterase Inhibitors: CH, chemistry
Phosphodiesterase Inhibitors: ME, metabolism
Phosphodiesterase Inhibitors: PD, pharmacology
*Pyrimidines: CS, chemical synthesis
Pyrimidines: CH, chemistry
Pyrimidines: ME, metabolism
Pyrimidines: PD, pharmacology
Pyrrolidinones: ME, metabolism
Rolipram
Structure-Activity Relationship
*Thiophenes: CS, chemical synthesis
Thiophenes: CH, chemistry
Thiophenes: ME, metabolism
Thiophenes: PD, pharmacology

CAS REGISTRY NO.: 60-92-4 (Cyclic AMP); 61413-54-5 (Rolipram)
CHEMICAL NAME: 0 (2-butyl-4-cyclohexylaminothieno(3,2-d)pyrimidine); 0 (Anti-Asthmatic Agents); 0 (Phosphodiesterase Inhibitors); 0 (Pyrimidines); 0 (Pyrrolidinones); 0 (Thiophenes); EC 3.1.4.- (phosphodiesterase III); EC 3.1.4.17 (3',5'-Cyclic-Nucleotide Phosphodiesterase); EC 3.1.4.17 (phosphodiesterase IV)

L115 ANSWER 12 OF 42 MEDLINE on STN
ACCESSION NUMBER: 1998350156 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9685237
TITLE: Synthesis and pharmacological activity of triazolo[1,5-a]triazine derivatives inhibiting eosinophilia.
AUTHOR: Akahoshi F; Takeda S; Okada T; Kajii M; Nishimura H; Sugiura M; Inoue Y; Fukaya C; Naito Y; Imagawa T; Nakamura N
CORPORATE SOURCE: Pharmaceutical Research Division, Yoshitomi Pharmaceutical Industries, Ltd., 2-25-1, Shodai-Ohtani, Hirakata, Osaka 573-1153, Japan.
SOURCE: Journal of medicinal chemistry, (1998 Jul 30) Vol. 41, No. 16, pp. 2985-93.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 28 Aug 1998
Last Updated on STN: 28 Aug 1998
Entered Medline: 17 Aug 1998

ABSTRACT:
In continuation of our previous work on eosinophilia inhibitors, we synthesized an additional series of inhibitors, which consisted of 5-amino-1-[(methylamino)thiocarbonyl]-1H-1,2,4-triazole derivatives and a newly developed series of 1,2,4-triazolo[1,5-a]-1,3,5-triazine derivatives. We evaluated their inhibitory activity on the airway eosinophilia model, which was induced by the intravenous (iv) injection of Sephadex particles. In the 1,2,4-triazole series

with various substituents at the 3 position of the triazole ring such as 2-furyl, pyridyl, and phenoxy, none of derivatives had comparable activity to the previously reported compound GCC-AP0341, 5-amino-3-(4-chlorophenyl)-1-[(methylamino)thiocarbonyl]-1H-1,2, 4-triazole. In the triazolo[1,5-a]triazine series, 2-(4-chlorophenyl)-6-methyl-1,2,4-triazolo[1,5-a]-1,3, 5-triazine-7(6H)-thione (3h) was highly potent, and when given orally it had an ID50 value of 0.3 mg/kg, which is comparable to that of GCC-AP0341. The fact that the structure-activity relationship of these two series was quite similar suggests that a common substructure, such as the 1,2,4-triazole ring with a substituted phenyl ring at the 3 position and a thiocarbonyl moiety at the 1 position, could contribute to the activity. Our selected compound 3h was less active than GCC-AP0341 in the antigen-induced hyper-responsiveness model in guinea pigs; however, we plan to carry out further studies on eosinophil functions, especially on their activation, using our two compounds, 3h and GCC-AP0341.

CONTROLLED TERM: Check Tags: Male
Animals
*Anti-Asthmatic Agents
Anti-Asthmatic Agents: CS, chemical synthesis
Anti-Asthmatic Agents: CH, chemistry
Anti-Asthmatic Agents: PD, pharmacology
Antigens, Helminth: IM, immunology
Ascaris: IM, immunology
Asthma: DT, drug therapy
Asthma: IM, immunology
Cell Count: DE, drug effects
Comparative Study
Dextrans: TO, toxicity
Drug Evaluation, Preclinical
Eosinophils: CY, cytology
Eosinophils: DE, drug effects
Guinea Pigs
Humans
In Vitro
Pulmonary Eosinophilia: CI, chemically induced
Pulmonary Eosinophilia: IM, immunology
*Pulmonary Eosinophilia: PC, prevention & control
Respiratory Hypersensitivity: DT, drug therapy
Respiratory Hypersensitivity: IM, immunology
Structure-Activity Relationship
*Triazines
Triazines: CS, chemical synthesis
Triazines: CH, chemistry
Triazines: PD, pharmacology
*Triazoles
Triazoles: CS, chemical synthesis
Triazoles: CH, chemistry
Triazoles: PD, pharmacology

CAS REGISTRY NO.: 9004-54-0 (Dextrans); 9014-76-0 (sephadex)

CHEMICAL NAME: 0 (2-(4-chlorophenyl)-6-methyl-1,2,4-triazolo(1,5-a)-1,3,5-triazine-7(6H)-thione); 0 (Anti-Asthmatic Agents); 0 (Antigens, Helminth); 0 (GCC-AP 0341); 0 (Triazines); 0 (Triazoles)

L115 ANSWER 13 OF 42 MEDLINE on STN

ACCESSION NUMBER: 1998296286 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9632360

TITLE: 7-Oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridines as novel inhibitors of human eosinophil phosphodiesterase.

AUTHOR: Duplantier A J; Andresen C J; Cheng J B; Cohan V L; Decker

C; DiCapua F M; Kraus K G; Johnson K L; Turner C R; UmLand J P; Watson J W; Wester R T; Williams A S; Williams J A
CORPORATE SOURCE: Central Research Division, Pfizer Inc, Groton, Connecticut 06340, USA.
SOURCE: Journal of medicinal chemistry, (1998 Jun 18) Vol. 41, No. 13, pp. 2268-77.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 16 Jul 1998
Last Updated on STN: 3 Mar 2000
Entered Medline: 9 Jul 1998

ABSTRACT:
High-throughput file screening against inhibition of human lung PDE4 led to the discovery of 3-ethyl-1-(4-fluorophenyl)-6-phenyl-7-oxo-4, 5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (11) as a novel PDE4 inhibitor. Subsequent SAR development, using an eosinophil PDE assay, led to analogues up to 50-fold more potent than 11 with IC50 values of 0.03-1.6 microM. One such compound, CP-220,629 (22) (IC50 = 0.44 microM), was efficacious in the guinea pig aerosolized antigen induced airway obstruction assay (ED50 2.0 mg/kg, po) and demonstrated a significant reduction in eosinophil (55%), neutrophil (65%), and IL-1beta (82%) responses to antigen challenge in atopic monkeys (10 mg/kg, po).

CONTROLLED TERM:
Airway Obstruction: IM, immunology
Airway Obstruction: ME, metabolism
Airway Obstruction: PA, pathology
Airway Obstruction: PC, prevention & control
Animals
*Anti-Asthmatic Agents
Anti-Asthmatic Agents: CS, chemical synthesis
Anti-Asthmatic Agents: CH, chemistry
Anti-Asthmatic Agents: PD, pharmacology
*Anti-Inflammatory Agents, Non-Steroidal
Anti-Inflammatory Agents, Non-Steroidal: CS, chemical synthesis
Anti-Inflammatory Agents, Non-Steroidal: CH, chemistry
Anti-Inflammatory Agents, Non-Steroidal: PD, pharmacology
Bronchoalveolar Lavage Fluid: CY, cytology
Bronchoalveolar Lavage Fluid: IM, immunology
Cell Count: DE, drug effects
Cell Line
Comparative Study
Cyclic AMP: ME, metabolism
Cytokines: ME, metabolism
*Dihydropyridines
Dihydropyridines: CS, chemical synthesis
Dihydropyridines: CH, chemistry
Dihydropyridines: PD, pharmacology
Drug Evaluation, Preclinical
Eosinophils: DE, drug effects
***Eosinophils: EN, enzymology**
Eosinophils: IM, immunology
Guinea Pigs
Humans
In Vitro
*Isoenzymes: AI, antagonists & inhibitors
Macaca fascicularis
Molecular Conformation

Searched by Barb O'Bryen, STIC 2-2518

Neutrophils: DE, drug effects
Neutrophils: IM, immunology
Ovalbumin: IM, immunology
*Phosphodiesterase Inhibitors
Phosphodiesterase Inhibitors: CS, chemical synthesis
Phosphodiesterase Inhibitors: CH, chemistry
Phosphodiesterase Inhibitors: PD, pharmacology
*Phosphoric Diester Hydrolases: ME, metabolism
*Pyrazoles
Pyrazoles: CS, chemical synthesis
Pyrazoles: CH, chemistry
Pyrazoles: PD, pharmacology
Pyrrolidinones: PD, pharmacology
Rolipram
Structure-Activity Relationship

CAS REGISTRY NO.: 60-92-4 (Cyclic AMP); 61413-54-5 (Rolipram); 9006-59-1 (Ovalbumin)

CHEMICAL NAME: 0 (Anti-Asthmatic Agents); 0 (Anti-Inflammatory Agents, Non-Steroidal); 0 (CP 220629); 0 (Cytokines); 0 (Dihydropyridines); 0 (Isoenzymes); 0 (Phosphodiesterase Inhibitors); 0 (Pyrazoles); 0 (Pyrrolidinones); EC 3.1.4 (Phosphoric Diester Hydrolases)

L115 ANSWER 14 OF 42 MEDLINE on STN
ACCESSION NUMBER: 94221594 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8168093
TITLE: Effects of sonicated eosinophils on the in vitro sensitivity of human lymphoma cells to glucose oxidase.
AUTHOR: Samoszuk M K; Nguyen V; Thomas C T; Jacobson D M
CORPORATE SOURCE: Pathology Department, University of California, Irvine 92717.
CONTRACT NUMBER: R29 CA 48713 (NCI)
SOURCE: Cancer research, (1994 May 15) Vol. 54, No. 10, pp. 2650-3. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199406
ENTRY DATE: Entered STN: 13 Jun 1994
Last Updated on STN: 3 Feb 1997
Entered Medline: 2 Jun 1994

ABSTRACT:
We report here that cultured human lymphoma cells in the absence of sonicated eosinophils are sensitive to killing by glucose oxidase (beta-D-glucose:oxygen-oxido reductase; EC 1.1.3.4) at concentrations as low as 0.025 microgram/ml, a level that can be rapidly attained in s.c. tumor implants in mice that receive a single nonlethal injection of enzyme. Multiple clonogenic assays were used to measure the survival of human lymphoma cell lines (H9 and ARH-77) cultured for 14 days in complete RPMI 1640 supplemented with exogenous glucose oxidase (0.025-2.5 micrograms/ml) or an immunoconjugate containing glucose oxidase (0.25-25 micrograms/ml) in the presence or absence of catalase (10 micrograms/ml) or an equal number of sonicated human eosinophils with or without supplemental 100 microM Br-, I-, or SCN-. In addition, we used an immunoassay to measure the concentration of glucose oxidase in s.c. implants of the Sp 2/0 myeloma tumor at 0-30 min after an i.v. injection of 50 micrograms of enzyme into 21 BALB/c mice. Doses of glucose oxidase as small as 0.025 microgram/ml killed more than 3 logs of tumor cells. Catalase completely inhibited, and sonicated human eosinophils partially inhibited, the killing by glucose oxidase or immunoconjugate, whereas supplemental halides had no effect.

Glucose oxidase i.v. produced levels > 0.04 microgram/g of tumor for 30 min after injection with a peak concentration of 0.079 microgram/g of tumor within 5 min of injection. These results are important because certain human lymphomas contain extensive extracellular deposits of eosinophil peroxidase, thereby making these tumors potentially less susceptible to killing by otherwise therapeutic doses of glucose oxidase.

CONTROLLED TERM: **Drug Screening Assays, Antitumor**
***Eosinophils: EN, enzymology**
Eosinophils: TR, transplantation
Glucose Oxidase: PK, pharmacokinetics
*Glucose Oxidase: PD, pharmacology
Half-Life
Humans
Lymphoma, B-Cell: EN, enzymology
*Lymphoma, B-Cell: TH, therapy
Lymphoma, T-Cell: EN, enzymology
*Lymphoma, T-Cell: TH, therapy
Research Support, U.S. Gov't, P.H.S.
Sonication
Tumor Cells, Cultured

CHEMICAL NAME: EC 1.1.3.4 (Glucose Oxidase)

L115 ANSWER 15 OF 42 MEDLINE on STN
ACCESSION NUMBER: 91079114 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1701767
TITLE: Terminal differentiation to mature neutrophils and eosinophils in suspension culture of the blast progenitors in acute myeloblastic leukemia.
AUTHOR: Nara N; Tohda S; Suzuki T; Nagata K; Yamashita Y; Imai Y; Morio T; Bessho M; Shibuya A; Adachi Y
CORPORATE SOURCE: First Department of Internal Medicine, Tokyo Medical and Dental University, Japan.
SOURCE: Hematologic pathology, (1990) Vol. 4, No. 3, pp. 125-34. Journal code: 8707764. ISSN: 0886-0238.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199101
ENTRY DATE: Entered STN: 22 Mar 1991
Last Updated on STN: 3 Feb 1997
Entered Medline: 31 Jan 1991

ABSTRACT:
The blasts obtained from three freshly diagnosed acute myeloblastic leukemia (AML) patients were cultured in suspension to determine whether leukemic blast progenitors can indeed differentiate to form mature granulocytes. One patient was AML M2. The other two patients were bilineal and biphenotypic leukemia, respectively. Media conditioned by human bladder carcinoma line 5637 (5637-CM) or recombinant human granulocyte colony-stimulating factor (rhG-CSF) was added to stimulate growth. In suspension, clonogenic cells grew for 1-3 weeks in two patients, while they did not increase in one patient. After repeated subculture, cells of blast morphology decreased in percentage and polymorphonuclear neutrophils, eosinophils, and monocyte-macrophages appeared. Lymphoid cell component of the patient 2, who was diagnosed as bilineal leukemia by dual-color immunofluorescence analysis, decreased in number after suspension culture and cells of myeloid phenotype became dominant. The findings show that clonogenic blast progenitors can renew themselves and can also undergo terminal differentiation to mature end cells.

CONTROLLED TERM: Adult
*Blast Crisis: PA, pathology

Cell Differentiation: PH, physiology
***Eosinophils: CY, cytology**
Granulocyte Colony-Stimulating Factor: PH, physiology
Humans
*Leukemia, Myelocytic, Acute: PA, pathology
*Neutrophils: CY, cytology
Recombinant Proteins: PH, physiology
Research Support, Non-U.S. Gov't
Tumor Cells, Cultured
Tumor Stem Cell Assay
*Tumor Stem Cells: PA, pathology
CAS REGISTRY NO.: 143011-72-7 (Granulocyte Colony-Stimulating Factor)
CHEMICAL NAME: 0 (Recombinant Proteins)

L115 ANSWER 16 OF 42 MEDLINE on STN
ACCESSION NUMBER: 89038612 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3184985
TITLE: Graded increase in probability of eosinophilic differentiation of HL-60 promyelocytic leukemia cells induced by culture under alkaline conditions.
AUTHOR: Fischkoff S A
CORPORATE SOURCE: Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia 19104-4283.
SOURCE: Leukemia research, (1988) Vol. 12, No. 8, pp. 679-86.
Journal code: 7706787. ISSN: 0145-2126.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198812
ENTRY DATE: Entered STN: 8 Mar 1990
Last Updated on STN: 29 Jan 1999
Entered Medline: 12 Dec 1988

ABSTRACT:
HL-60 cells differentiate primarily to eosinophils instead of neutrophils when cultured with butyric acid if they have previously been cultured under alkaline conditions (pH 7.6). To determine the nature of the process by which this occurs, a group of single-cell derived clones was produced from HL-60 cells after prolonged passage under alkaline conditions. When these clones were induced to mature with butyric acid, each clone demonstrated a characteristic proportion of mature eosinophils and neutrophils. This property was stable for multiple passages. Subclones derived from these clones also demonstrated the same probability of differentiating to an eosinophil as their parent clones. Reversion toward neutrophilic differentiation gradually occurred after several months of culture under conditions of reduced pH. The most highly directed clones demonstrated 90-95% eosinophilic differentiation and continued to differentiate primarily to eosinophils after seven months of culture at the reduced pH. Thus, in HL-60 cells, the tendency to differentiate to an eosinophil is a long-lived, heritable, continuously variable phenotype that is inducible in cells by culture under alkaline conditions. This tendency persists for prolonged periods after the alkaline conditions are removed, but may gradually revert toward neutrophilic differentiation with time.
CONTROLLED TERM: Agar
Butyric Acid
Butyric Acids
*Cell Differentiation
Cell Line
Cell Transformation, Neoplastic: PA, pathology
*Culture Media
***Eosinophils: PA, pathology**

Humans
Hydrogen-Ion Concentration
*Leukemia, Promyelocytic, Acute: PA, pathology
Probability
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, Non-P.H.S.
***Tumor Cells, Cultured: PA, pathology**
Tumor Stem Cell Assay

CAS REGISTRY NO.: 107-92-6 (Butyric Acid); 9002-18-0 (Agar)
CHEMICAL NAME: 0 (Butyric Acids); 0 (Culture Media)

L115 ANSWER 17 OF 42 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2006-577786 [59] WPIX
DOC. NO. NON-CPI: N2006-464934
DOC. NO. CPI: C2006-179083
TITLE: **Degranulation** reaction or cytokine production controlling agent for preventing/treating inflammatory, allergic and autoimmune diseases, comprises substance that controls intracellular concentration of zinc ion, as active ingredient.
DERWENT CLASS: B04 B05 D16 S03
INVENTOR(S): HIRANO, T; NISHIDA, K
PATENT ASSIGNEE(S): (RIKE) RIKEN KK
COUNTRY COUNT: 113
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2006080581	A1	20060803	(200659)*	JA	83	A61K045-00

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KN KP KR KZ LC LK LR LS LT LU LV LY MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2006080581	A1	WO 2006-JP1932	20060131

PRIORITY APPLN. INFO: JP 2005-23196 20050131
INT. PATENT CLASSIF.:
MAIN: A61K045-00
SECONDARY: A61K031-4402; A61P037-00; A61P037-02; A61P037-08; A61P043-00; C12Q001-02; G01N033-15; G01N033-50

BASIC ABSTRACT:
WO2006080581 A UPAB: 20060914
NOVELTY - A **degranulation** reaction controlling agent or cytokine production controlling agent (I), comprises a substance capable of controlling the intracellular concentration of zinc ion, as an active ingredient.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a drug (II) for preventing and treating inflammatory disease, an allergic disease and/or autoimmune disease, comprising (I) or a substance capable of controlling the intracellular concentration of zinc ion, as an active ingredient;

(2) controlling (M1) **degranulation** reaction or cytokine production, involves:

(a) carrying out in **vitro** control of intracellular concentration of zinc ion, or

(b) administering a substance capable of controlling the concentration of zinc ions in a cell;

(3) screening (M2) a compound capable of controlling **degranulation** reaction or cytokine production, involves measuring the intracellular concentration of zinc ion;

(4) use of the substance (III) capable of controlling the intracellular concentration of zinc ion for manufacturing the **degranulation** reaction controlling agent and cytokine production controlling agent, and for manufacturing a drug for preventing and treating inflammatory disease, allergic diseases and/or an autoimmune disease; and

(5) preventing and treating (M3) inflammatory disease, an allergic disease and/or autoimmune disease, involves administering a substance capable of controlling the concentration of zinc ion in cells.

ACTIVITY - Antiinflammatory; Antiallergic; Immunosuppressive; Dermatological; Antiarthritic; Antirheumatic; Nephrotropic; Antipyretic; Respiratory-Gen.; Endocrine-Gen.; Antianemic; Neuroprotective; Antipsoriatic; Hepatotropic; Gastrointestinal-Gen.

In vivo analysis of ability of zinc ion chelator in treating allergic diseases in a mouse model was carried out as follows. Balb/cAJc1 (6 week old) female mice ear was subcutaneously administered with an IgE antibody (SPE-7) (0.5 mu g). After 12 hours, zinc ion chelator (e.g. N,N,N',N'-tetrakis (2-pyridyl methyl) ethylenediamine (TPEN)) was administered to the abdominal cavity of mice. After 30 minutes, dinitrophen-bovine serum albumin (DNP-BSA, antigen) (250 mu g) was intravenously administered to the tail, to induce passive skin anaphylaxis. Evans blue (1.25 mg) was administered to the mice. The Evans blue dye was extracted from the mice using formamide. The extracted dye was measured at the wavelength of 620 nm. The results showed that the zinc ion chelator significantly suppressed Evans blue leakage. The zinc ion chelator thus significantly suppressed type I allergy response.

MECHANISM OF ACTION - Controls intracellular zinc ion concentration; Controls **degranulation** reaction or cytokine production.

USE - (I) or the method is useful for controlling **degranulation** reaction or cytokine production. The screening method is useful for screening a compound capable of controlling **degranulation** reaction or cytokine production. The drug or treatment method is useful for preventing and treating inflammatory disease, allergic disease and/or an autoimmune disease. The substance is useful for manufacturing the **degranulation** reaction controlling agent and cytokine production controlling agent, and for manufacturing a drug for preventing and treating inflammatory disease, allergic diseases and/or an autoimmune disease. (All claimed).

(I) is useful for treating and preventing systemic lupus erythematosus, connective tissue disease, rheumatoid arthritis, Sjogren's syndrome, rheumatic fever, Good pasture's syndrome, Hashimoto's disease, Addison's disease, autoimmune hemolytic anemia, Crohn's disease, multiple sclerosis, psoriasis, hepatitis, etc.

DESCRIPTION OF DRAWING(S) - The figure is a graph representing the effect of N,N,N',N'-tetrakis (2-pyridyl methyl) ethylenediamine (TPEN) zinc ion against type I allergy response (passive skin anaphylaxis).

Dwg.4/4

FILE SEGMENT: CPI EPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B04-F04B; B04-L01; B04-N04; B04-N13; B05-A01B; B05-A03A4; B06-D02; B07-D04C; B10-A09B; B10-B01B; B11-C08E; B11-C10; **B12-K04E1**; B14-C03; B14-C04; B14-C06; B14-C09B; B14-D01; B14-E10C1; B14-F03; B14-G02; B14-K01; B14-N10; B14-N11; B14-N12; B14-N17; B14-S01; D05-H09
EPI: S03-E14A1
TECH UPTX: 20060914

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Agent: In the agent (I), the substance capable of controlling zinc ion concentration is a substance capable of controlling the expression and/or function of a zinc ion-requiring protein or zinc ion transporter. The zinc ion-requiring protein is chosen from Raf-1, protein kinase C alpha (PKCalpha), GEF-H1, histone deacetylase (HDAC), SQSTM1, ubiquitin-protein ligase E3, ubiquitin conjugation protein E2, metallothionein, phosphatase, Snail, tumor necrosis factor receptor-associated factor-6 (TRAF6), Paxillin, Zyxin and Jade-1. The zinc ion transporter is chosen from LIV of human ZIP(s) and human cation diffusion facilitators (CDF(s)) family. The cell is chosen from neutrophil, **eosinophil**, basophilic, mast cell, natural killer cell, natural killer T cell, cytotoxic T cell and blood platelets, preferably mast cell.
Preferred Method: In the method (M1), the concentration of zinc ion is controlled by zinc ion or zinc ion chelator. The concentration of zinc ion is controlled by controlling the expression and/or function of a zinc ion-requiring protein or zinc ion transporter.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Agent: In the agent (I), the substance capable of controlling zinc ion concentration is zinc ion or zinc ion chelator, where the zinc ion is introduced into a cell using zinc ionophore. The zinc ion chelator is chosen from 2, 3-dimercapto-1-propane sulfonic acid (DMPS), N,N,N',N'-tetrakis (2-pyridyl methyl) ethylenediamine (TPEN), EDTA and N-(6-methoxy-8-quinolyl)-p-toluenesulfonamide (TSQ).

L115 ANSWER 18 OF 42 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2006-559143 [57] WPIX
DOC. NO. NON-CPI: N2006-448815
DOC. NO. CPI: C2006-174342
TITLE: Identifying a compound that interferes with dendritic cell (DC) differentiation and/or maturation for the treatment of asthma, involves measuring influence of an liver X receptor agonist on differentiation and/or maturation of DCs.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): BELANGER, C; DARTEIL, R; HUM, D
PATENT ASSIGNEE(S): (GENF-N) GENFIT SA
COUNTRY COUNT: 113
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2006077012	A2	20060727	(200657)*	EN	66	G01N033-50

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KN KP KR KZ LC LK LR LS LT LU LV LY MA MD MG MK MN MW MX MZ NA

NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2006077012	A2	WO 2006-EP43	20060105

PRIORITY APPLN. INFO: EP 2005-888 20050118
INT. PATENT CLASSIF.:
MAIN: G01N033-50
SECONDARY: A61K031-00; A61P011-00; A61P011-06
BASIC ABSTRACT:
WO2006077012 A UPAB: 20060906
NOVELTY - Identifying a compound that interferes with dendritic cell (DC) differentiation and/or maturation, involves stimulating differentiation of DC (precursors) to DCs or DC maturation, adding liver X receptor (LXR) agonist stimulating receptor to DCs, measuring effects of the LXR agonist on differentiation or maturation of the DC (precursors) and comparing the results with that of a reference compound, and identifying the LXR agonist, is new.

DETAILED DESCRIPTION - Identifying (M1) a compound that interferes with (inhibit or prevent) dendritic cell (DC) differentiation and/or maturation, involves:

(a) stimulating in vitro differentiation of DC precursors to DCs and/or DC maturation;

(b) adding during, before or after step (a), to the DCs or DC precursors an liver X receptor (LXR) agonist stimulating receptor;

(c) measuring the influence of the LXR agonist on the differentiation and/or maturation of the DC precursors or DCs;

(d) optionally repeating step (a)-(c), where instead of LXR agonist, a reference compound known to inhibit the differentiation and/or maturation is added during, before or after step (a), and measuring the influence of the reference compound on the differentiation and/or maturation of the DC precursors or DCs and comparing these results with the results obtained in step (c);

(e) identifying an LXR agonist interfering with (inhibiting or preventing) DC differentiation and/or maturation from the results of step (c) and/or (d); and

(f) optionally, isolating and/or formulating the compound identified in step (e).

INDEPENDENT CLAIMS are included for:

(1) identifying (M2) LXR-mediated, DC specific, anti-inflammatory target genes, involves:

(a) stimulating in vitro the differentiation of DC precursors to DCs and/or the DC maturation;

(b) adding during, before or after step (a) to the DCs or DC precursors an LXR agonist stimulating the receptor;

(c) analyzing the influence (positive or negative) of the LXR agonist on the expression of secondary genes (target genes), by comparing the expression of the same genes in DC precursors or DCs which were not treated by the LXR agonist;

(d) optionally repeating steps (a)-(c) where instead of LXR agonist, a reference compound known to induce the differentiation and/or maturation is added during, before or after step (a);

(e) optionally, comparing the results of steps (c) and (d);

(f) identifying an LXR mediated target gene, where the expression of the target gene is down- or up-regulated upon the treatment using the LXR

agonist;

(g) optionally, isolating a nucleic acid representing at least part of the target gene, and (h) optionally further identifying compounds having an activity on the expression of the target gene identified in step (f) or on the activity of the protein encoded by the target gene;

(2) use of a non-human mammalian animal (A1) as an in vivo model for:

(3) (a) identifying compounds inhibiting Th2-cytokine secretion, recruitment of inflammatory cells to the bronchoalveolar lavage (BAL) fluid, and/or peribronchial and/or perivascular infiltration of inflammatory cells;

(4) (b) identifying compounds preventing Th2-cytokine secretion, recruitment of inflammatory cells to the BAL fluid, and/or peribronchial and/or perivascular infiltration of inflammatory cells;

(5) (c) identifying compounds inhibiting T-cell proliferation and/or Th2-cytokine release through the analysis of the primary response; or

(6) (d) identifying compounds inhibiting the recruitment of inflammatory cells to the BAL fluid, Th2 cytokine secretion, and/or peribronchial and/or perivascular infiltration of inflammatory cells;

(7) use of an LXR agonist (A2) to interfere in vitro with (inhibit or prevent) DC precursor differentiation and/or DC maturation, or being identified by the method (M1) or (M2), or by using the animal (A1) for the preparation of a medicament for the treatment of a disease associated with the recruitment of inflammatory cells to the BAL fluid, increased Th2-cytokine release or peribronchial and/or perivascular infiltration of inflammatory cells; and

(8) an isolated DC composition or an isolated DC precursor composition (C1), comprising DCs or DC precursors which have been treated in vitro with an LXR agonist interfering with (inhibiting or preventing) DC precursor differentiation and/or DC maturation.

ACTIVITY - Antiasthmatic.

MECHANISM OF ACTION - Inhibitor of DC differentiation and/or maturation; LXR-Agonist; Cytokine secretion-Inhibitor.

Bone marrow-derived DCs were treated with T-0901317 before the pulse with ovalbumin (OVA). The OVA-pulsed DCs were injected intratracheally into allergic asthma model mice. Ten days later, the mice received 3 consecutive OVA aerosol challenges. At day 13, the BAL fluid was analyzed for cellular content and the thoracic lymph nodes were extracted, restimulated with OVA for 4 days, and analyzed for cytokine secretion. The results showed that the treatment of DCs with T-0901317 reduced the number of macrophages, lymphocytes and **eosinophils**, and also reduced the levels of Th2-cytokines, IL-4 and IL-5 produced by T-cell.

USE - The method (M1) is useful for identifying a compound that interferes with (inhibit or prevent) dendritic cell (DC) differentiation and/or maturation. The animal (A1) being a mouse or a rat is useful for identifying compounds inhibiting or preventing Th2-cytokine secretion, recruitment of inflammatory cells to the BAL fluid, and/or peribronchial and/or perivascular infiltration of inflammatory cells, identifying compounds inhibiting T-cell proliferation and/or Th2-cytokine release through the analysis of the primary response, and identifying compounds inhibiting the recruitment of inflammatory cells to the BAL fluid, Th2 cytokine secretion, and/or peribronchial and/or perivascular infiltration of inflammatory cells. The animal (A1) is also useful as a model for identifying compounds interfering with (inhibiting or preventing) asthma, more particularly allergy-induced asthma. The LXR agonist (A2) is useful for the preparation of a medicament for the treatment of a disease associated with the recruitment of inflammatory cells to the BAL fluid, increased Th2-cytokine release or peribronchial and/or perivascular infiltration of inflammatory cells such as asthma, more preferably allergy-induced asthma. The composition (C1) is useful for studying the recruitment of inflammatory cells to the BAL fluid in a model organism,

the Th2-cytokine release in the BAL fluid and/or by lymph node cells in a model organism, the peribronchial and/or perivascular infiltration of inflammatory cells in a model organism, and asthma, more preferably allergy-induced asthma (claimed).

ADVANTAGE - The methods (M1) and (M2) are high throughput screening methods.

Dwg.0/11

FILE SEGMENT: CPI EPI
FIELD AVAILABILITY: AB
MANUAL CODES: CPI: B04-E12; B04-F02; B04-K01; B04-P01A; B11-C08E; B11-C08F4; B11-C10; **B12-K04E1**; B12-K04F; B14-K01A; B14-L01; B14-L06; D05-H08; D05-H09; D05-H12A
EPI: S03-E09F; S03-E14A1

TECH UPTX: 20060906

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: In method (M1), the DC or DC precursor is of myeloid, lymphoid or plasmacytoid origin. The DC is directly isolated from peripheral or cord blood. The DC precursor is a monocyte, a CD34+ hematopoietic progenitor cell or an interleukin-3 receptor (IL-3R) plasmacytoid cell. The DC differentiates from a monocyte. The DC precursor is isolated from peripheral blood, cord blood, bone marrow, thymus or lymphoid tissues. The stimulation of the differentiation of the DC precursors to DCs or the maturation of the DCs in step (a) is achieved by treating with an agent chosen from allergens, inflammatory cytokines, CD40 ligand, bacterial products, pathogens such as Escherichia coli, **Candida**, viruses or other agents. The LXR agonist is identified using a binding assay and/or a signal transduction assay specific for the receptor. The DC precursor differentiation to DCs is measured through the analysis of cell surface expression of CD1a, CD11c, CD40, human leukocyte antigen (HLA)-DR, transcription of CD40 and/or matrix metalloproteinase 9 (MMP9) and/or other differentiation marker. The maturation of DCs is measured through the analysis of the lipopolysaccharide (LPS) (or other maturation agents) inducible expression of cell surface markers CD83, CD86, CD80, HLA-DR and/or through the analysis of the transcription of chemokines interferon-inducible protein of 10 kDa (IP-10), 'EBl1 ligand chemokine (ELC), monocyte chemoattractant protein (MCP)-1, regulated upon activation, normal T-cell expressed and secreted (RANTES), thymus and activation-regulated chemokine (TARC), chemokine receptor CCR7 and/or other maturation agent. The expression is analyzed through quantitative reverse transcriptase-PCR (RT-PCR) analysis or by fluorescence activated cell sorter (FACS) analysis. The DC precursor differentiation or DCs maturation is measured through the analysis of T-cell immune response triggered by DCs. The T-cell immune response is measured in a heterologous mixed lymphocytes reaction (MLR) assay, thus incubating DCs with allogeneic T-cells and measuring T-cell proliferation. The LXR agonist of step (b) or the reference compound of step (d) is T0901317 or GW3965, or its functional equivalent, or combination.
In method (M2), the influence of step (c) is analyzed through the analysis of the expression of a large battery of genes through quantitative RT-PCR analysis.
Preferred Animal: (A1) being useful as an in vivo model for:
(a) identifying compounds inhibiting Th2-cytokine secretion, recruitment of inflammatory cells to the bronchoalveolar lavage (BAL) fluid, and/or peribronchial and/or perivascular infiltration of inflammatory cells, involves sensitizing the animal by injecting ovalbumin (OVA) emulsified in alum thus generating OVA-specific T-cells in a non-human mammalian animal, incubating the animal for several days, challenging the animal with OVA aerosols, injecting an LXR agonist before each aerosol challenge in the animal, analyzing the inflammatory cells content of the BAL fluid of the animal, analyzing Th2-cytokine secretion by T-cells of the animal,

measuring the level of Th2-cytokine secretion in the BAL fluid, analyzing peribronchial and/or perivascular inflammatory cell infiltration in lung biopsies of the animal, identifying compounds as LXR agonists inhibiting Th2-cytokine secretion, recruitment of inflammatory cells to the BAL fluid, and/or peribronchial and/or perivascular infiltration of inflammatory cells, and optionally isolating and/or formulating the identified compound;
(b) identifying compounds preventing Th2-cytokine secretion, recruitment of inflammatory cells to the BAL fluid, and/or peribronchial and/or perivascular infiltration of inflammatory cells, involves injecting an LXR agonist in a non-human mammalian animal, sensitizing the animal by injecting OVA emulsified in alum thus generating OVA-specific T-cells in the animal, incubating the animal for several days, challenging the animal with OVA aerosols, optionally injecting an LXR agonist before each aerosol challenge in the animal, analyzing the inflammatory cells content of the BAL fluid of the animal, analyzing Th2-cytokine secretion by T-cells of the animal, measuring the level of Th2-cytokine secretion in the BAL fluid, analyzing peribronchial and/or perivascular inflammatory cell infiltration in lung biopsies of the animal, identifying compounds as LXR agonists preventing Th2-cytokine secretion, recruitment of inflammatory cells to the BAL fluid and/or peribronchial and/or perivascular infiltration of inflammatory cells, and optionally isolating and/or formulating the identified compound;
(c) identifying compounds inhibiting T-cell proliferation and/or Th2-cytokine release through the analysis of the primary response, involves isolating OVA-specific T-cells from the TCR transgenic mouse DO11.10, labeling the obtained OVA-specific T-cells with carboxyfluorescein succinimidyl ester (CFSE), treating DCs in vitro with an LXR agonist, pulsing the DCs with OVA, injecting the CFSE-labeled T-cells in a non-human mammalian animal, analyzing T-cell proliferation and/or Th2-cytokine secretion by ex vivo OVA-restimulated T-cells, comparing T-cell proliferation and/or Th2-cytokine production analyzed in the above step with T-cell proliferation and/or Th2-cytokine production in an animal treated as described in the above steps, where the DCs were not treated with an LXR agonist, optionally comparing T-cell proliferation and/or Th2-cytokine production analyzed in the analyzing step with T-cell proliferation and/or Th2-cytokine production in an animal treated as described in the above steps, where the DCs were treated with a reference compound, identifying compounds as LXR agonists inhibiting T-cell proliferation and/or Th2- cytokine release, and optionally isolating and/or formulating the identified compound.
Identifying compounds inhibiting the recruitment of inflammatory cells to the BAL fluid, Th2 cytokine secretion, and/or peribronchial and/or perivascular infiltration of inflammatory cells, involves:
(a) treating DCs with an LXR agonist;
(b) pulsing the DCs with OVA;
(c) injecting the LXR-treated DCs pulsed with OVA in the non human mammalian animal;
(d) incubating the animal for several days;
(e) challenging the animal with OVA aerosols;
(f) analyzing inflammatory cell content of the BAL fluid of the animal;
(g) optionally extracting draining lymph nodes from the animal;
(h) optionally restimulating lymph nodes with OVA;
(i) optionally analyzing Th2-cytokine secretion produced by the cells of restimulating step;
(j) optionally measuring Th2-cytokine secretion in the BAL fluid;
(k) optionally analyzing peribronchial and/or perivascular inflammatory cell infiltration in lung biopsies of the animal;
(l) comparing the cellular content of step (f) Th2-cytokine secretion optionally measured in step (i) or (j), and/or peribronchial and/or

perivascular inflammatory cell infiltration optionally measured in step (k) with the cellular content, Th2-cytokine secretion, and/or peribronchial and/or perivascular inflammatory cell infiltration obtained from an animal treated as described in the above steps, where the DCs were not stimulated with the LXR agonist, or optionally the DCs were stimulated with a reference compound;
(m) identifying the LXR agonist as a compound inhibiting recruitment of inflammatory cells to the BAL fluid, Th2-cytokine secretion, and/or peribronchial and/or perivascular infiltration of inflammatory cells, if the LXR agonist reduces the cellular content, reduces Th2-cytokine production as determined in step (i') or (j) and/or reduces peribronchial and/or perivascular inflammatory cell infiltration of step (k); and
(n) optionally isolating and/or formulating the compound identified in step (m).

L115 ANSWER 19 OF 42 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-316464 [33] WPIX
CROSS REFERENCE: 2003-074982 [07]; 2004-214171 [20]
DOC. NO. NON-CPI: N2001-227462
DOC. NO. CPI: C2001-097553
TITLE: Novel G-protein coupled receptor polypeptide and polynucleotide for treating cancer, autoimmune, pulmonary, cardiovascular and neurological disorders and for identifying modulators useful for treating asthma.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): AUBART, K M; BERGSMA, D J; FITZGERALD, L R; GRAYBILL, T L; LI, X; MICHALOVICH, D; MORROW, D M; ZHU, Y
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP; (SMIK) SMITHKLINE BEECHAM PLC
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2001033221	A1	20010510	(200133)*	EN	54	G01N033-53
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE						
W: CA JP US						
EP 1226435	A1	20020731	(200257)	EN		G01N033-53
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE						
JP 2003512854	W	20030408	(200333)		74	C12N015-09

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001033221	A1	WO 2000-US29461	20001026
EP 1226435	A1	EP 2000-973867	20001026
		WO 2000-US29461	20001026
JP 2003512854	W	WO 2000-US29461	20001026
		JP 2001-535055	20001026

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1226435	A1 Based on	WO 2001033221
JP 2003512854	W Based on	WO 2001033221

PRIORITY APPLN. INFO: US 2000-497790 20000203; US 1999-431898 19991102

Searched by Barb O'Bryen, STIC 2-2518

INT. PATENT CLASSIF.:
MAIN: C12N015-09; G01N033-53
SECONDARY: A01N037-18; A61K031-7088; A61K038-00; A61K039-395; A61K045-00; A61K048-00; A61P001-00; A61P003-10; A61P009-10; A61P011-00; A61P011-06; A61P013-00; A61P013-12; A61P019-02; A61P025-00; A61P025-16; A61P025-18; A61P025-22; A61P025-24; A61P025-28; A61P029-00; A61P029-02; A61P031-04; A61P031-12; A61P037-02; A61P037-08; C07H021-04; C07K001-00; C07K002-00; C07K004-00; C07K005-00; C07K007-00; C07K014-00; C07K014-705; C07K016-00; C07K016-28; C07K017-00; C12N001-15; C12N001-19; C12N001-20; C12N001-21; C12N005-00; C12N005-02; C12N005-10; C12N015-00; C12N015-63; C12N015-70; C12N015-74; C12P021-02; C12P021-04; C12P021-06; G01N033-15; G01N033-50; G01N033-567

BASIC ABSTRACT:

WO 200133221 A UPAB: 20040324

NOVELTY - An isolated G-protein coupled receptor polypeptide, AXOR35 (I) comprising a sequence of 390 amino acids, (its 95% identical sequence, fragments or variants) encoded by a polynucleotide comprising a sequence (S1) of 1173 base pairs fully defined in the specification, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated polynucleotide (II) encoding (I) or its 95% identical sequence, selected from a polynucleotide sequence comprising a nucleotide sequence of (S1), a polynucleotide having 95% sequence identity to (S1), a nucleotide sequence of 100 nucleotides obtained by screening a library under stringent hybridization conditions with a labeled probe having the sequence of (II) or its fragment of at least 15 nucleotides, RNA equivalent of (II), complementary polynucleotide, variants and fragments of (II);

(2) preparation of (I);

(3) an expression vector present in a compatible host cell, comprising (II);

(4) producing (M1) a recombinant host cell, by transforming a cell with an expression vector comprising (II), such that the host cell under appropriate culture conditions produces (I);

(5) a recombinant host cell (III) produced by (M1);

(6) a membrane of (III) expressing (I);

(7) an antibody immunospecific for (I);

(8) screening (M2) for AXOR35 polypeptides, antagonists or agonists, by:

(a) incubating a labeled histamine and histamine-like compound with a whole cell expressing AXOR35 polypeptide on the cell surface, or cell membrane containing AXOR35 polypeptide;

(b) measuring the amount of labeled histamine or a histamine-like compound bound to the cell or its membrane;

(c) adding a candidate compound to a mixture of labeled histamine or histamine-like compound and the cell or its membrane and allowing to equilibrium to be attained;

(d) measuring the amount of labeled histamine or histamine-like compound bound to the whole cell or cell membrane; and

(e) comparing the difference in the labeled histamine or histamine-like compound bound, such that the compound which causes the reduction in binding is an agonist or antagonist;

(9) identifying (M3) agonists or antagonists of AXOR35 polypeptides, by:

(a) contacting a cell expressing the polypeptide on the surface, being associated with a second component capable of providing a detectable

signal in response to the binding of a compound to the polypeptide, with a compound to be screened under conditions to permit binding to the polypeptide and determining whether the compound binds to and activates or inhibits the polypeptide by measuring or comparing the level of signal generated from the interaction of the compound with the polypeptide with the level of signal without the presence of the compound; or

(b) determining inhibition of binding of a ligand to cells which have the polypeptide on the surface or to cell membranes containing the polypeptide, in the presence of a candidate compound under conditions, to permit binding to the polypeptide, and determining the amount of ligand bound to the polypeptide, such that a compound capable of causing reduction of binding of a ligand is an agonist or antagonist;

(10) treating diseases, by administering to a patient an agonist or an antagonists identified by (M3); and

(11) agonizing or antagonizing AXOR35 to inhibit or promote the function of lymphocytes, macrophages, **eosinophils** or neutrophils in diseased tissue, by administering AXOR35 agonists or antagonists identified by the above methods.

ACTIVITY - Antibacterial; Antiviral; Antifungal; Anti-HIV; Protozoacide; Antiasthmatic; Antiulcer; Antidiarrheic; Antiinflammatory; Antiallergic; Antiarthritic; Antirheumatic; Hypotensive; Hypertensive; Antipsoriatic; Neuroprotective; Cytostatic; Osteopathic; Nootropic; Antiatherosclerotic; Antiparkinsonian; Anorectic; Dermatological; Cerebroprotective; Antidiabetic; Neuroleptic. Test details are described but no results given.

MECHANISM OF ACTION - Gene therapy; Vaccine; AXOR35 polypeptide modulator.

USE - (I) is useful for identifying agonists or antagonists of AXOR35 polypeptide, which are useful for treating asthma and inhibiting or promoting the function of lymphocytes, macrophages, **eosinophils** or neutrophils in asthmatic lung (claimed). AXOR35 polypeptides and polynucleotides are useful for treating bacterial, fungal, protozoan and viral infections, particularly, infections caused by HIV, gastrointestinal disorders, such as gastric or duodenal ulcer, diarrhea, inflammatory bowel diseases such as Crohn's disease, ulcerative colitis, inflammation such as pruritis and atopic dermatitis, allergies and allergic disorders, autoimmune disorders including rheumatoid arthritis, psoriasis, multiple sclerosis, cardiovascular diseases, such as angina pectoris, myocardial infarction, hypotension, hypertension, pulmonary disorders such as chronic obstructive pulmonary disease, cough, renal diseases, atherosclerosis, psychotic and neurological disorders, including migraine, anorexia, anxiety, schizophrenia, depression, dyskinesias, such as Parkinson's diseases, cancers including leukemia and other diseases such as type II diabetes, obesity, stroke, graft versus host disease, septic shock and osteoporosis. AXOR35 polynucleotides are useful as diagnostic reagents, by detecting mutations in the associated gene, for chromosome localization and tissue expression studies and for producing transgenic animals useful in **drug discovery.** The polypeptides and polynucleotides are also useful as vaccine. The polypeptides are useful as immunogens to produce antibodies which are useful for treating diseases.

Dwg.0/0

FILE SEGMENT: CPI EPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-E03D; B04-E08; B04-F0100E; B04-G04; B04-K01; B11-C07A; B12-K04A; B12-K04F; B14-A01; B14-A02; B14-A02B1; B14-A03; **B14-A04A**; B14-C03; B14-C09; B14-E02; B14-E08; B14-E11; B14-E12; B14-F02A; B14-F02B; B14-F07; B14-G02A; B14-J01; B14-J01A; B14-J01A3; B14-J01B3; B14-K01A; B14-L01; B14-L06; B14-N17C; B14-S03; B14-S04; B14-S11;

D05-H07; D05-H09; D05-H11; D05-H12A; D05-H12E; D05-H14
EPI: S03-E14H4
TECH UPTX: 20010615
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation: (I) is prepared by culturing host cell transfected with (II) and recovering the expressed polypeptide (claimed).
Preferred Method: (M3) further comprises identifying agonists or antagonists in the presence of a labeled or unlabeled histamine or histamine-like compound.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) may be prepared synthetically by using solid phase peptide synthesizers.

L115 ANSWER 20 OF 42 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2006286800 EMBASE
TITLE: Modulation of allergic immune responses by mucosal application of recombinant lactic acid bacteria producing the major birch pollen allergen Bet v 1.
AUTHOR: Daniel C.; Repa A.; Wild C.; Pollak A.; Pot B.; Breiteneder H.; Wiedermann U.; Mercenier A.
CORPORATE SOURCE: Dr. U. Wiedermann, Department of Specific Prophylaxis and Tropical Medicine, Center for Physiology and Pathophysiology, Kinderspitalgasse 15, 1090 Vienna, Austria
SOURCE: Allergy: European Journal of Allergy and Clinical Immunology, (2006) Vol. 61, No. 7, pp. 812-819. .
Refs: 41
ISSN: 0105-4538 E-ISSN: 1398-9995 CODEN: LLRGDY
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
015 Chest Diseases, Thoracic Surgery and Tuberculosis
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 5 Jul 2006
Last Updated on STN: 5 Jul 2006

ABSTRACT: Background: Probiotic lactic acid bacteria (LAB) are able to modulate the host immune system and clinical trials have demonstrated that specific strains have the capacity to reduce allergic symptoms. Therefore, we aimed to evaluate the potential of recombinant LAB producing the major birch pollen allergen Bet v 1 for mucosal vaccination against birch pollen allergy. Methods: Recombinant Bet v 1-producing Lactobacillus plantarum and Lactococcus lactis strains were constructed. Their immunogenicity was compared with purified Bet v 1 by subcutaneous immunization of mice. Intranasal application of the live recombinant strains was performed to test their immunomodulatory potency in a mouse model of birch pollen allergy. Results: Bet v 1 produced by the LAB was recognized by monoclonal anti-Bet v 1 and IgE antibodies from birch pollen-allergic patients. Systemic immunization with the recombinant strains induced significantly lower IgG1/IgG2a ratios compared with purified Bet v 1. Intranasal pretreatment led to reduced allergen-specific IgE vs enhanced IgG2a levels and reduced interleukin (IL)-5 production of splenocytes in vitro, indicating a shift towards non-allergic T-helper-1 (Th1) responses. Airway inflammation, i.e. eosinophils and IL-5 in lung lavages, was reduced using either Bet v 1-producing or control strains. Allergen-specific secretory IgA

responses were enhanced in lungs and intestines after pretreatment with only the Bet v 1-producing strains. Conclusions: Mucosal vaccination with live recombinant LAB, leading to a shift towards non-allergic immune responses along with enhanced allergen-specific mucosal IgA levels offers a promising approach to prevent systemic and local allergic immune responses. .COPYRGT. 2006 Blackwell Munksgaard.

CONTROLLED TERM: Medical Descriptors:
*allergy: DT, drug therapy
*immune response
lactic acid bacterium
allergic asthma: DT, drug therapy
pollen allergy: DT, drug therapy
birch
vaccination
Lactobacillus plantarum
Lactobacillus delbrueckii
immunogenicity
immunomodulation
statistical significance
airway
eosinophil
lung lavage
Th1 cell
in vitro study
spleen cell
lung
intestine
bacterial strain
drug screening
drug potency
drug purification
cytokine production
nonhuman
female
mouse
animal experiment
animal model
controlled study
animal cell
article
priority journal

CONTROLLED TERM: Drug Descriptors:
*pollen antigen: DO, drug dose
*pollen antigen: DT, drug therapy
*pollen antigen: NA, intranasal drug administration
*pollen antigen: PD, pharmacology
*pollen antigen: SC, subcutaneous drug administration
*pollen allergen bet v 1: DO, drug dose
*pollen allergen bet v 1: DT, drug therapy
*pollen allergen bet v 1: NA, intranasal drug administration
*pollen allergen bet v 1: PD, pharmacology
*pollen allergen bet v 1: SC, subcutaneous drug administration
immunoglobulin E antibody
immunoglobulin G1
immunoglobulin G2a
immunoglobulin A
unclassified drug

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ACCESSION NUMBER: 2006011068 EMBASE

TITLE: Preparation and biological evaluation of indole, benzimidazole, and thienopyrrole piperazine carboxamides: Potent human histamine H(4) antagonists.

AUTHOR: Venable J.D.; Cai H.; Chai W.; Dvorak C.A.; Grice C.A.; Jablonowski J.A.; Shah C.R.; Kwok A.K.; Ly K.S.; Pio B.; Wei J.; Desai P.J.; Jiang W.; Nguyen S.; Ling P.; Wilson S.J.; Dunford P.J.; Thurmond R.L.; Lovenberg T.W.; Karlsson L.; Carruthers N.I.; Edwards J.P.

CORPORATE SOURCE: J.D. Venable, Johnson and Johnson Pharmaceutical Research and Development, L.L.C., 3210 Merryfield Row, San Diego, CA 92121, United States. jvenable@prdus.jnj.com

SOURCE: Journal of Medicinal Chemistry, (29 Dec 2005) Vol. 48, No. 26, pp. 8289-8298. .
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ISSN: 0022-2623 CODEN: JMCMAR

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DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 26 Jan 2006
Last Updated on STN: 26 Jan 2006

ABSTRACT: Three series of H(4) receptor ligands,- derived from indoly-2-yl-(4-methyl-piperazin-1-yl)-methanones, have been synthesized and their structure-activity relationships evaluated for activity at the H (4) receptor in competitive binding and functional assays. In all cases, substitution of small lipophilic groups in the 4 and 5-positions led to increased activity in a [(3)H]histamine radiolabeled ligand competitive binding assay. In vitro metabolism and initial pharmacokinetic studies were performed on selected compounds leading to the identification of indole 8 and benzimidazole 40 as potent H(4) antagonists with the potential for further development. In addition, both 8 and 40 demonstrated efficacy in in vitro mast cell and eosinophil chemotaxis assays. .COPYRGT. 2005 American Chemical Society.

CONTROLLED TERM: Medical Descriptors:
*drug synthesis
***drug screening**
*drug receptor binding
drug mechanism
structure activity relation
drug structure
drug activity
radioassay
in vitro study
drug metabolism
drug efficacy
mast cell
eosinophil
chemotaxis
human
nonhuman
mouse
rat

controlled study
human cell
animal cell
article
Drug Descriptors:
*indole derivative: AN, drug analysis
*indole derivative: DV, drug development
*indole derivative: PD, pharmacology
*benzimidazole derivative: AN, drug analysis
*benzimidazole derivative: DV, drug development
*benzimidazole derivative: PD, pharmacology
*thienopyrrole piperazine carboxamide derivative: AN, drug analysis
*thienopyrrole piperazine carboxamide derivative: DV, drug development
*thienopyrrole piperazine carboxamide derivative: PD, pharmacology
*histamine H4 receptor
*antihistaminic agent: AN, drug analysis
*antihistaminic agent: DV, drug development
*antihistaminic agent: PD, pharmacology
indoly 2 yl (4 methylpiperazin 1 yl)methanone derivative: AN, drug analysis
indoly 2 yl (4 methylpiperazin 1 yl)methanone derivative: DV, drug development
indoly 2 yl (4 methylpiperazin 1 yl)methanone derivative: PD, pharmacology
tritium
histamine
5 chloroindole: AN, drug analysis
5 chloroindole: DV, drug development
5 chloroindole: PD, pharmacology
(5 chloro 1h benzoimidazol 2 yl)(4 methylpiperazin 1 yl)methanone: AN, drug analysis
(5 chloro 1h benzoimidazol 2 yl)(4 methylpiperazin 1 yl)methanone: DV, drug development
(5 chloro 1h benzoimidazol 2 yl)(4 methylpiperazin 1 yl)methanone: PD, pharmacology
unclassified drug
jnj 7777120
jnj 10191584

CAS REGISTRY NO.: (histamine H4 receptor) 272100-58-0; (tritium) 10028-17-8; (histamine) 51-45-6, 56-92-8, 93443-21-1

CHEMICAL NAME: Jnj 7777120; Jnj 10191584

L115 ANSWER 22 OF 42 EMBASE

ACCESSION NUMBER: 2004368980 EMBASE

TITLE: In vitro effects of flunisolide on MMP-9, TIMP-1, fibronectin, TGF-β1 release and apoptosis in sputum cells freshly isolated from mild to moderate asthmatics.

AUTHOR: Profita M.; Gagliardo R.; Di Giorgi R.; Bruno A.; Riccobono L.; Bonanno A.; Bousquet J.; Vignola A.M.

CORPORATE SOURCE: A.M. Vignola, Ist. di Med. Generale e Pneumologia, Universita di Palermo, Via Trabucco 180, 90146 Palermo, Italy

SOURCE: Allergy: European Journal of Allergy and Clinical Immunology, (2004) Vol. 59, No. 9, pp. 927-932. .
Refs: 38
ISSN: 0105-4538 CODEN: LLRGDY

COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Sep 2004
Last Updated on STN: 16 Sep 2004

ABSTRACT: Background: Corticosteroids play an important role in inflammation and remodelling of airways and are considered an important therapeutic target in asthma. Inflammation in asthma is characterized by a dysregulation of eosinophil apoptosis and of markers of airways remodelling. We evaluated the ability of flunisolide to inhibit in vitro the release of metalloproteinases-9 (MMP-9), tissue inhibitor metalloproteinases-1 (TIMP-1), transforming growth factor (TGF-β) and fibronectin by sputum cells (SC) as well as to induce sputum eosinophil apoptosis. Methods: The SC, isolated from induced sputum samples of 12 mild-to-moderate asthmatics, were cultured for 24 h in the presence or absence of flunisolide (1, 10 and 100 μM). The release of mediators was assessed by enzyme-linked immunosorbent assay (ELISA) whereas apoptosis was studied by TUNEL technique. Results: Flunisolide (10 μM) significantly reduced MMP-9 and TIMP-1 ($P = 0.0011$ and $P < 0.0001$ respectively) and increased MMP-9/TIMP-1 molar ratio ($P = 0.004$). In addition, flunisolide decreased TGF-β and fibronectin release by SC ($P = 0.006$; and $P < 0.0001$ respectively) and increased eosinophil apoptosis ($P < 0.001$). Conclusions: These results demonstrate that flunisolide may play an important role in the inhibition of airway inflammation and remodelling, by promoting the resolution of eosinophilic inflammation and by inhibiting the release of MMP-9, TIMP-1, TGF-β and fibronectin.

CONTROLLED TERM: Medical Descriptors:
*cytokine release
*apoptosis
*sputum analysis
*asthma: DT, drug therapy
*cell isolation
drug effect
drug screening
in vitro study
eosinophil
sputum culture
enzyme linked immunosorbent assay
nick end labeling
analytic method
human
male
female
clinical article
controlled study
human cell
adult
article
priority journal
Drug Descriptors:
*flunisolide: DT, drug therapy
*flunisolide: PD, pharmacology
*gelatinase B: EC, endogenous compound
*tissue inhibitor of metalloproteinase 1: EC, endogenous compound

*fibronectin: EC, endogenous compound
*transforming growth factor beta1: EC, endogenous compound
CAS REGISTRY NO.: (flunisolide) 3385-03-3; (gelatinase B) 146480-36-6; (tissue inhibitor of metalloproteinase 1) 140208-24-8; (fibronectin) 86088-83-7

L115 ANSWER 23 OF 42 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2004520191 EMBASE
TITLE: Selective phosphodiesterase type 4 inhibitors reduce the prolonged survival of eosinophils stimulated by granulocyte-macrophage colony-stimulating factor.
AUTHOR: Takeuchi M.; Tatsumi Y.; Kitaichi K.; Baba K.; Suzuki R.; Shibata E.; Takagi K.; Miyamoto K.-I.; Hasegawa T.; Takagi K.
CORPORATE SOURCE: K. Takagi, Department of Medical Technology, Nagoya University, School of Health Sciences, 1-1-20 Daikominami, Higashi-ku, Nagoya 461-8673, Japan. kztakagi@met.nagoya-u.ac.jp
SOURCE: Biological and Pharmaceutical Bulletin, (2002) Vol. 25, No. 2, pp. 184-187. .
Refs: 28
ISSN: 0918-6158 CODEN: BPBLEO
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 28 Dec 2004
Last Updated on STN: 28 Dec 2004

ABSTRACT: It is well known that bronchial asthma is defined as chronic eosinophilic inflammation of the respiratory tract and that as one of the various types of inflammatory cells, eosinophils induce the airway inflammation of chronic asthma. Granulocyte-macrophage colony-stimulating factor (GM-CSF) has been shown to play an important role in the prolongation of the survival of eosinophils. We investigated the inhibitory effect of the selective phosphodiesterase (PDE) 4 inhibitors, 3,4-dipropyl-4,5,7,8-tetrahydro-3H-imidazo[1,2-i]purin-5-one (XT-611) and rolipram, and the nonselective PDE inhibitor theophylline, against GM-CSF-induced prolongation of the survival of eosinophils isolated from patients with bronchial asthma. Eosinophils (10(6) cells/ml) were incubated in the presence of GM-CSF together with or without theophylline, rolipram or XT-611 at 37°C, and the viable cells were assessed up to 4 d using Trypan blue dye exclusion. The presence of theophylline (10(-4) M), rolipram (10(-4)-10(-5)M) or XT-611 (10 (-4)-10(-5)M) significantly reduced the GM-CSF (10 pg/ml)-induced prolongation of viability of eosinophils. These findings suggest that selective PDE 4 inhibitors, including XT-611, may effectively reduce the activities of inflammatory cells in the airway of bronchial asthma patients.

CONTROLLED TERM: Medical Descriptors:
***eosinophil**
***cell survival**
cell isolation
cell viability
drug screening
asthma
human
male

female
clinical article
controlled study
human cell
article
Drug Descriptors:
*granulocyte macrophage colony stimulating factor
*rolipram: CM, drug comparison
*rolipram: PD, pharmacology
*3,4 dipropyl 4,5,7,8 tetrahydro 3h imidazo[1,2 i]purin 5 one: CM, drug comparison
*3,4 dipropyl 4,5,7,8 tetrahydro 3h imidazo[1,2 i]purin 5 one: DV, drug development
*3,4 dipropyl 4,5,7,8 tetrahydro 3h imidazo[1,2 i]purin 5 one: PD, pharmacology
*phosphodiesterase IV inhibitor: CM, drug comparison
*phosphodiesterase IV inhibitor: DV, drug development
*phosphodiesterase IV inhibitor: PD, pharmacology
*theophylline: CM, drug comparison
*theophylline: PD, pharmacology
trypan blue
unclassified drug
xt 611

CAS REGISTRY NO.: (rolipram) 61413-54-5; (theophylline) 58-55-9, 5967-84-0, 8055-07-0, 8061-56-1, 99007-19-9; (trypan blue) 72-57-1
CHEMICAL NAME: Xt 611
COMPANY NAME: Sigma (United States)

L115 ANSWER 24 OF 42 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2002095020 EMBASE
TITLE: Differential inhibition of inflammatory effector functions by petasin, isopetasin and neopetasin in human eosinophils.
AUTHOR: Thomet O.A.R.; Wiesmann U.N.; Blaser K.; Simon H.-U.
CORPORATE SOURCE: H.-U. Simon, Department of Pharmacology, University of Bern, Friedbuhlstrasse 49, CH-3010 Bern, Switzerland. hus@pki.unibe.ch
SOURCE: Clinical and Experimental Allergy, (2001) Vol. 31, No. 8, pp. 1310-1320. .
Refs: 44
ISSN: 0954-7894 CODEN: CLEAEN
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 21 Mar 2002
Last Updated on STN: 21 Mar 2002

ABSTRACT: Background: Priming of eosinophils with granulocyte-macrophage colony-stimulating factor (GM-CSF) and subsequent stimulation with platelet-activating factor (PAF) or the anaphylatoxin C5a is associated with a rapid production of leukotrienes (LTs) and release of eosinophil cationic protein (ECP). Objective: This study was designed to determine the effects of the sesquiterpene esters petasin, isopetasin and neopetasin on LT generation and ECP release in eosinophils in vitro. Methods: The model of eosinophil activation described above was used to induce LT production and ECP release. Cells were incubated with petasins and control inhibitors prior to priming and stimulation. To analyse intracellular steps of eosinophil activation and determine potential drug targets, some key signalling events were studied.

Activity of cytosolic phospholipase A(2) (cPLA(2)) was measured by analysing the generation of arachidonic acid (AA). Translocation of 5-lipoxygenase (5-LO) was observed using immunofluorescence microscopy. Intracellular calcium concentrations [Ca(2+)](i) were measured by a bulk spectrofluorometric assay. Results: Whereas all three compounds inhibited LT synthesis, ECP release from eosinophils was blocked by petasin only, but not isopetasin or neopetasin. Similarly, PAF- or C5a-induced increases in [Ca(2+)](i) were completely abrogated by petasin only, whereas isopetasin and neopetasin had significant lower blocking efficacy. Moreover, only petasin, but not isopetasin or neopetasin, prevented increases in cPLA(2) activity and 5-LO translocation from the cytosolic compartment to the nucleus envelope in calcium ionophore-stimulated eosinophils. Conclusion: These data suggest that different petasins may at least partially block different intracellular signalling molecules. To reduce LT synthesis, isopetasin and neopetasin may act at the level of or distal to 5-LO. In contrast, petasin may inhibit inflammatory effector functions in human eosinophils by disrupting signalling events at the level of or proximal to phospholipase Cβ (PLCβ), besides its potential inhibitory activity within mitogen-activated protein kinase (MAPK) and LT pathways.

CONTROLLED TERM: Medical Descriptors:
***eosinophil**
drug effect
in vitro study
drug screening
drug targeting
signal transduction
enzyme activity
drug structure
treatment outcome
drug efficacy
immunofluorescence microscopy
calcium cell level
spectrofluorometry
cell nucleus membrane
enzyme inhibition
human
controlled study
human cell
article
priority journal
Drug Descriptors:
*petasin: CM, drug comparison
*petasin: DV, drug development
*petasin: PD, pharmacology
*isopetasin: CM, drug comparison
*isopetasin: DV, drug development
*isopetasin: PD, pharmacology
*neopetasin: CM, drug comparison
*neopetasin: DV, drug development
*neopetasin: PD, pharmacology
*plant extract: CM, drug comparison
*plant extract: DV, drug development
*plant extract: PD, pharmacology
*sesquiterpene derivative: CM, drug comparison
*sesquiterpene derivative: DV, drug development
*sesquiterpene derivative: PD, pharmacology
phospholipase A2: EC, endogenous compound
arachidonic acid: EC, endogenous compound
arachidonate 5 lipoxygenase: EC, endogenous compound

calcium ion: EC, endogenous compound
leukotriene: EC, endogenous compound
eosinophil cationic protein: EC, endogenous compound
mitogen activated protein kinase: EC, endogenous compound
calcimycin
unclassified drug

CAS REGISTRY NO.: (petasin) 26577-85-5; (isopetasin) 469-26-1; (phospholipase A2) 9001-84-7; (arachidonic acid) 506-32-1, 6610-25-9, 7771-44-0; (arachidonate 5 lipoxygenase) 80619-02-9; (calcium ion) 14127-61-8; (mitogen activated protein kinase) 142243-02-5; (calcimycin) 52665-69-7

L115 ANSWER 25 OF 42 EMBASE

ACCESSION NUMBER: 2000440139 EMBASE
TITLE: A mass balance study to evaluate the biotransformation and excretion of [(14)C]-triamcinolone acetonide following oral administration.
AUTHOR: Argenti D.; Jensen B.K.; Hensel R.; Bordeaux K.; Schleimer R.; Bickel C.; Heald D.
CORPORATE SOURCE: Dr. D. Argenti, Aventis Pharmaceuticals, Medical Affairs, Clin. Pharmacol./Pharmacokinetics, 500 Arcola Road, Collegeville, PA 19426, United States
SOURCE: Journal of Clinical Pharmacology, (2000) Vol. 40, No. 7, pp. 770-780. .
Refs: 29
ISSN: 0091-2700 CODEN: JCPCBR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 5 Jan 2001
Last Updated on STN: 5 Jan 2001

ABSTRACT: The principle objective of this study was to characterize the absorption, metabolism, and disposition of orally administered [(14)C]-triamcinolone acetonide. Six healthy male subjects each received a single 100 μCi (.simeq.800 μg) oral dose of [(14)C]-triamcinolone acetonide. Plasma, urine, and fecal samples were collected at selected times and analyzed for triamcinolone acetonide and [(14)C]-derived radioactivity. Plasma protein binding of triamcinolone acetonide was also determined. Metabolite profiling and identification were carried out in plasma and excreta. Principle metabolites were assessed for activity with in vitro anti-inflammatory models. [(14)C]-triamcinolone acetonide was found to be systemically absorbed following oral administration. The presystemic metabolism and clearance of triamcinolone acetonide were extensive, with only a small fraction of the total plasma radioactivity being made up of triamcinolone acetonide. Little to no parent compound was detected in the plasma 24 hours after administration. Most of the urinary and fecally [(14)C]-derived radioactivity was also excreted within 24 and 72 hours postdose, respectively. Mean plasma protein binding of triamcinolone acetonide was constant, predictable, and a relatively low 68% over a 24-fold range of plasma concentrations. Three principle metabolites of triamcinolone acetonide were profiled in plasma, urine, and feces. These metabolites were identified as 6β-hydroxy triamcinolone, 21-carboxylic acid triamcinolone acetonide, and 6β-hydroxy-21-oic triamcinolone acetonide. All three metabolites failed to show any concentration-dependent effects in anti-inflammatory models evaluating IL-5-sustained eosinophil viability and IgE-induced basophil histamine release. (C) 2000 the American College of Clinical Pharmacology.

CONTROLLED TERM: Medical Descriptors:
*drug transformation
***drug screening**
*drug excretion
drug absorption
drug metabolism
drug disposition
drug protein binding
antiinflammatory activity
drug clearance
radioactivity
histamine release
eosinophil
cell viability
basophil
area under the curve
human
male
human experiment
normal human
clinical trial
phase 1 clinical trial
article
Drug Descriptors:
*carbon 14
*triamcinolone acetonide: CT, clinical trial
*triamcinolone acetonide: PK, pharmacokinetics
*triamcinolone acetonide: PD, pharmacology
*triamcinolone acetonide: PO, oral drug administration
drug metabolite
6beta hydroxy triamcinolone
21 carboxylic acid triamcinolone acetonide
6beta hydroxy 21 oic triamcinolone acetonide
interleukin 5
glucocorticoid
unclassified drug

CAS REGISTRY NO.: (CARBON 14) 14762-75-5; (triamcinolone acetonide) 76-25-5

L115 ANSWER 26 OF 42 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001009738 EMBASE
TITLE: Interleukin-5: A drug target for allergic diseases.
AUTHOR: Sanderson C.J.; Urwin D.
CORPORATE SOURCE: C.J. Sanderson, Dept. of Molecular Immunology, Western Australian Inst. Med. Res., Curtin University of Technology, Rear 50 Murray Street, Perth 6000, WA, Australia. colin@cyllene.uwa.edu.au
SOURCE: Current Opinion in Investigational Drugs, (2000) Vol. 1, No. 4, pp. 435-441. .
Refs: 54
ISSN: 0967-8298 CODEN: CIDREE
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 026 Immunology, Serology and Transplantation
015 Chest Diseases, Thoracic Surgery and Tuberculosis
005 General Pathology and Pathological Anatomy
037 Drug Literature Index
030 Pharmacology
LANGUAGE: English

Searched by Barb O'Bryen, STIC 2-2518

SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19 Jan 2001
Last Updated on STN: 19 Jan 2001

ABSTRACT: There is a large body of evidence that eosinophils are a key component of the allergic response in asthma. Interleukin (IL) 5 is uniquely involved in the production of eosinophils, and with a variety of other cytokines and factors controls their activation, localization and survival. Thus, IL-5 is an important drug target for new anti-asthmatics. The routes to drug discovery are based on screens for inhibitors of IL-5 production, ligand antagonists, control of receptor expression and receptor activation. In this review, we will discuss specific targets and screening assays with examples of some of the compounds in development.

CONTROLLED TERM: Medical Descriptors:
*allergic disease: ET, etiology
*allergic disease: DT, drug therapy
*asthma: ET, etiology
*asthma: DT, drug therapy
human
clinical trial
nonhuman
eosinophil
cell activation
protein localization
cell survival
drug screening
T lymphocyte
drug inhibition
cytokine production
drug mechanism
experimental model
drug half life
review
Drug Descriptors:
*interleukin 5: EC, endogenous compound
*antiasthmatic agent: DV, drug development
*antiasthmatic agent: PD, pharmacology
*antiasthmatic agent: DT, drug therapy
*antiasthmatic agent: PO, oral drug administration
*antiasthmatic agent: CT, clinical trial
*antiasthmatic agent: IV, intravenous drug administration
*antiasthmatic agent: PK, pharmacokinetics
cytokine: EC, endogenous compound
glucocorticoid: DT, drug therapy
glucocorticoid: PD, pharmacology
cyclosporin A: DT, drug therapy
cyclosporin A: PD, pharmacology
tsukubaenolide: DT, drug therapy
tsukubaenolide: PD, pharmacology
rapamycin: DT, drug therapy
rapamycin: PD, pharmacology
cyclosporin derivative: DT, drug therapy
cyclosporin derivative: PD, pharmacology
cyclosporin derivative: DV, drug development
om 01: DT, drug therapy
om 01: PD, pharmacology
om 01: DV, drug development
phthalimide derivative: DV, drug development
phthalimide derivative: PD, pharmacology
m 50367: DV, drug development

m 50367: PD, pharmacology
m 50367: DT, drug therapy
m 50367: PO, oral drug administration
suplatast tosylate: PD, pharmacology
suplatast tosylate: DT, drug therapy
3 [4 (8 fluoro 5,11 dihydrobenz[b]oxepino[4,3 b]pyridin 11 ylidene)piperidino]propionic acid: PD, pharmacology
3 [4 (8 fluoro 5,11 dihydrobenz[b]oxepino[4,3 b]pyridin 11 ylidene)piperidino]propionic acid: DT, drug therapy
uracil derivative: PD, pharmacology
uracil derivative: DV, drug development
uracil derivative: DT, drug therapy
azauracil: PD, pharmacology
azauracil: DV, drug development
azauracil: DT, drug therapy
r 146225: DV, drug development
r 146225: PD, pharmacology
r 146225: DT, drug therapy
antisense oligonucleotide: PD, pharmacology
antisense oligonucleotide: DT, drug therapy
antisense oligonucleotide: IV, intravenous drug administration
oligodeoxynucleotide phosphorothioate: PD, pharmacology
oligodeoxynucleotide phosphorothioate: DT, drug therapy
oligodeoxynucleotide phosphorothioate: IV, intravenous drug administration
monoclonal antibody: PD, pharmacology
monoclonal antibody: DT, drug therapy
monoclonal antibody: DV, drug development
monoclonal antibody: CT, clinical trial
monoclonal antibody: PK, pharmacokinetics
sch 55700: PD, pharmacology
sch 55700: DT, drug therapy
sch 55700: DV, drug development
sch 55700: CT, clinical trial
sch 55700: PK, pharmacokinetics
sb 240563: PD, pharmacology
sb 240563: DT, drug therapy
sb 240563: DV, drug development
sb 240563: CT, clinical trial
sb 240563: PK, pharmacokinetics
isothiazole derivative: DV, drug development
isothiazole derivative: PD, pharmacology
isothiazole derivative: DT, drug therapy
unclassified drug
mepolizumab

CAS REGISTRY NO.: (cyclosporin A) 59865-13-3, 63798-73-2; (tsukubaenolide) 104987-11-3; (rapamycin) 53123-88-9; (suplatast tosylate) 94055-76-2; (3 [4 (8 fluoro 5,11 dihydrobenz[b]oxepino[4,3 b]pyridin 11 ylidene)piperidino]propionic acid) 161522-25-4, 188199-97-5; (azauracil) 461-89-2

CHEMICAL NAME: (1) Tacrolimus; (2) Fk 506; (3) M 50367; (4) Ipd 1151t; (5) Hsr 609; (6) R 146225; (7) Sch 55700; (8) Sb 240563; (9) Mepolizumab; Om 01

COMPANY NAME: (2) Fujisawa; (3) Mochida; (4) Taiho; (5) Hokuriku; (6) Janssen; (7) Celltech; (9) SmithKline Beecham; Isis

L115 ANSWER 27 OF 42 EMBASE

ACCESSION NUMBER: 82132141 EMBASE

DOCUMENT NUMBER: 1982132141
TITLE: Effect of corticosteroids on antigen induced histamine release in asthmatic patients.
AUTHOR: Tobisawa S.
CORPORATE SOURCE: III Dep. Int. Med., Iwate Med. Univ., Sch. Med., Morioka, Japan
SOURCE: Journal of the Japan Broncho-Esophagological Society, (1982) Vol. 33, No. 1, pp. 37-44. .
CODEN: NKSGAH
COUNTRY: Japan
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
015 Chest Diseases, Thoracic Surgery and Tuberculosis
026 Immunology, Serology and Transplantation
LANGUAGE: Japanese
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 9 Dec 1991
Last Updated on STN: 9 Dec 1991

ABSTRACT: In order to clarify the inhibitory effects of corticosteroid on the histamine release in vitro with house dust antigen, intravenous administration of corticosteroid to asthmatic patients was performed. Histamine release on challenge with house dust antigen was suppressed: By intravenous administration of 4 mg dexamethasone in 10 asthmatics. The inhibition rate was 24% and 60% at intervals of 3 and 6 hours, respectively; by intravenous administration of 1000 mg hydrocortisone in 5 asthmatics. The inhibition rate was 53%, 54% at intervals of 3 and 6 hours, respectively; and by intravenous administration of 30 mg prednisolone in 5 asthamatics. The inhibition rate was 52.3%, 21% at intervals of 6 and 24 hours, respectively. The inhibition rate reached a maximum extent in 6 hours after the intravenous administration of various corticosteroids. Basophil count was reduced to a significantly low level after the intravenous administration of various corticosteroids. Eosinophil count was reduced to a significantly low level after the intravenous administration of either dexamethasone or hydrocortisone. After the intravenous administration of various corticosteroids, neither released histamine levels nor whole blood histamine levels correlated with basophil count. The above results suggest that the histamine release in vitro with house dust antigen in asthmatic patients was inhibited by corticosteroids such as dexamethasone, hydrocortisone, prednisolone.

CONTROLLED TERM: Medical Descriptors:
*asthma
*basophil
***eosinophil**
*histamine release
drug screening
in vitro study
major clinical study
therapy
respiratory system
intravenous drug administration
drug comparison
blood and hemopoietic system
Drug Descriptors:
*antigen
*corticosteroid
*dexamethasone
*hydrocortisone
*prednisolone
house dust allergen
CAS REGISTRY NO.: (dexamethasone) 50-02-2; (hydrocortisone) 50-23-7;

(prednisolone) 50-24-8

L115 ANSWER 28 OF 42 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 82121780 EMBASE
DOCUMENT NUMBER: 1982121780
TITLE: Biological activities of leukotriene B4.
AUTHOR: Smith M.J.H.
CORPORATE SOURCE: Dept. Chem. Pathol., King's Coll. Hosp. Med. Sch., London SE5 8RX, United Kingdom
SOURCE: Agents and Actions, (1981) Vol. 11, No. 6-7, pp. 571-572. . CODEN: AGACBH
COUNTRY: Switzerland
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Dec 1991
Last Updated on STN: 9 Dec 1991
CONTROLLED TERM: Medical Descriptors:
*chemotaxis
*dose response
*drug release
***drug screening**
***eosinophil**
*human
*macrophage
*monocyte
*neutrophil
*rabbit
*skin
cytotaxin
drug comparison
gas chromatography
high performance liquid chromatography
reversed phase liquid chromatography
preliminary communication
in vitro study
human cell
animal experiment
blood and hemopoietic system
histology
normal human
drug response
Drug Descriptors:
*calcimycin
*leukotriene
*prostaglandin e2
arachidonic acid derivative
CAS REGISTRY NO.: (calcimycin) 52665-69-7; (prostaglandin e2) 363-24-6

L115 ANSWER 29 OF 42 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 79193758 EMBASE
DOCUMENT NUMBER: 1979193758
TITLE: Specific inhibition of the polymorphonuclear leukocyte chemotactic response to hydroxy-fatty acid metabolites of arachidonic acid by methyl ester derivatives.
AUTHOR: Goetzl E.J.; Valone F.H.; Reinhold V.N.; Gorman R.R.
CORPORATE SOURCE: Howard Hughes Med. Inst., Lab. Harvard Med. Sch., Boston, Mass. 02115, United States

SOURCE: Journal of Clinical Investigation, (1979) Vol. 63, No. 6, pp. 1181-1186. .
CODEN: JCINAO
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
026 Immunology, Serology and Transplantation
025 Hematology
030 Pharmacology
LANGUAGE: English

ABSTRACT: The human polymorphonuclear (PMN) leukocytes chemotactic activity of the hydroxy-fatty acid metabolites of arachidonic acid, 12-L-hydroxy-5,8,10-heptadecatrienoic acid (HHT) and 12-L-hydroxy 5,8,10,14-eicosatetraenoic acid (HETE), is eliminated by methylation. Both methyl esters are specific competitive inhibitors of the PMN leukotactic responses to the parent stimuli, and exert no effects on the responses to formyl-methionyl peptides or chemotactic fragments of the fifth component of complement. 50% inhibition of the in vitro chemotactic responses of PMN leukocytes HETE and HHT was achieved by equimolar concentration of the corresponding methyl esters, whereas reciprocal cross-inhibition was observed at molar ratios of HETE methyl ester to HHT and HHT methyl ester to HETE which reflected to the three- to fivefold greater chemotactic potency of HETE relative to HHT. Methyl esters of structurally related, but no chemotactic, fatty acids did not competitively inhibit the chemotaxis elicited by HETE or HHT. The intaperitoneal injection of HETE in guinea pigs evoked an eosinophil response at 30 min and a neutrophil response at 5 h, which were prevented by a one- to twofold molar ratio of HETE methyl ester. The competitive inhibition of the in vitro chemotactic activity and the in vivo leukotactic effect of the unsaturated hydroxy-fatty acids by homologous methyl ester derivatives suggests that the cellular component of natural inflammatory reactions may be susceptible to specific regulation by receptor-directed modulation of the activity of the predominant chemotactic principles.

CONTROLLED TERM: Medical Descriptors:
*12 hydroxy 5,8,10 heptadecatrienoic acid
*chemotaxis
*drug antagonism
*drug comparison
***drug screening**
*granulocyte
*structure activity relation
eosinophil
guinea pig
formylmethionylleucylphenylalanine h 3
n formylnorleucylleucylphenylalanine h 3
pharmacokinetics
neutrophil
intraperitoneal drug administration
in vitro study
theoretical study
animal experiment
histology
blood and hemopoietic system
Drug Descriptors:
*12 hydroxyicosatetraenoic acid
*arachidonic acid
*hydroxy fatty acid
*indometacin
methylnitronitrosoguanidine
CAS REGISTRY NO.: (12 hydroxyicosatetraenoic acid) 54397-83-0, 59985-28-3,

71030-37-0; (arachidonic acid) 506-32-1, 6610-25-9, 7771-44-0; (indometacin) 53-86-1, 74252-25-8, 7681-54-1; (methylnitronitrosoguanidine) 70-25-7
COMPANY NAME: Elysian (United States); Merck (United States); Aldrich (United States)

L115 ANSWER 30 OF 42 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 77029415 EMBASE
DOCUMENT NUMBER: 1977029415
TITLE: Chemotactic migration of neutrophils under agarose.
AUTHOR: John T.J.; Sieber Jr. O.F.
CORPORATE SOURCE: Dept. Ped., Univ. Arizona Med. Cent., Tucson, Ariz. 85724, United States
SOURCE: Life Sciences, (1976) Vol. 18, No. 2, pp. 177-182. .
CODEN: LIFSAK
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
025 Hematology
005 General Pathology and Pathological Anatomy
030 Pharmacology
LANGUAGE: English
ABSTRACT: A simple test for neutrophil chemotaxis is described. Wells were cut in soft agarose gel and filled with human peripheral blood leukocytes, chemotactin and control substances. Neutrophils consistently migrated under agarose towards the well with chemotactin, but not towards wells with control substances. Chemotaxis was quantitated as the mean distance travelled by 10 cells farthest from the well of origin, at specified time intervals after filling the wells. Approximately 1/3 distance was covered in 2 hours, 3/4 in 4 hours and 90 per cent in 6 hours. The migrating cells examined after fixation and staining were found to be predominantly neutrophils with occasional eosinophils and monocytes.

CONTROLLED TERM: Medical Descriptors:
*blood
*chemotaxis
***drug screening**
***eosinophil**
*human
*leukocyte
*monocyte
*neutrophil
theoretical study
methodology
in vitro study
normal human
histology

L115 ANSWER 31 OF 42 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2006-18274 DRUGU B P
TITLE: A new chemical tool for exploring the role of the PDE4D isozyme in leukocyte function.
AUTHOR: Chambers R J; Abrams K; Castleberry T A; Cheng J B; Fisher D A; Kamath A V; Marfat A; Nettleton D O; Pillar J D; et-al.
CORPORATE SOURCE: Pfizer
LOCATION: Cambridge, MA, USA
SOURCE: Bioorg.Med.Chem.Lett. (16, No. 3, 718-21, 2006) 1 Fig. 3 Tab. 0 Ref.
CODEN: BMCLE8 ISSN: 0960-894X
AVAIL. OF DOC.: Pfizer Inc, Res Technol Ctr, 620 Mem Dr, Cambridge, MA, USA,

02139. (Chambers R J, 15 Authors, e-mail: Robert.J.Chambers@pfizer.com).
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

The inhibitory effect of rolipram (1) and nicotinamide (2) against PDE4 was ***evaluated.*** **Compound** (2) effectively elevated intracellular cAMP and blocked the release of **eosinophil** associated mediators ***eosinophil*** derived **neurotoxin** (EDN) and cysteinyl leukotrienes (LTE4) in human whole blood. However, (2) was ineffective in blocking the release of monocyte-associated mediator TNF-alpha from human whole blood compared to (1). These findings demonstrate that PDE4D inhibitor (2) is an effective chemical tool implicating PDE4D in playing a unique role in ***eosinophil*** chemotaxis and mediator release.

SECTION HEADING: B Biochemistry
P Pharmacology

CLASSIF. CODE: 14 Enzyme Inhibitors
20 Immunological

CONTROLLED TERM:
[01] NICOTINAMIDE *PH; NICOTINAM *RN; ROLIPRAM *RC; VITAMINS-B *FT; NITRIC-OXIDE-SYNTHASE-INHIBITORS *FT; IN-**VITRO** *FT; U937-CELL *FT; HUMAN *FT; EC-3.1.4.17 *FT; INHIBITION *FT; PHOSPHODIESTERASE-INHIBITOR *FT; **EOSINOPHIL** *FT; LEUKEMIA *FT; TUMOR-CELL *FT; TISSUE-**CULTURE** *FT; 3+,5+-CYCLIC-NUCLEOTIDE-PHOSPHODIESTERASE *FT; LEUKOCYTE *FT; PH *FT
CAS REGISTRY NO.: 98-92-0
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L115 ANSWER 32 OF 42 PASCAL COPYRIGHT 2006 INIST-CNRS. ALL RIGHTS RESERVED.
on STN DUPLICATE 1
ACCESSION NUMBER: 1999-0081207 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 1999 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Increased levels of **interleukin** 5 are associated with the generation of eosinophilia in drug-induced hypersensitivity syndrome
AUTHOR: CHOQUET-KASTYLEVSKY G.; INTRATOR L.; CHENAL C.; BOCQUET H.; REVUZ J.; ROUJEAU J.-C.
CORPORATE SOURCE: Department of Dermatology, Hopital Henri Mondor, Universite Paris XII, Creteil, France; Department of Immunology, Hopital Henri Mondor, Universite Paris XII, Creteil, France
SOURCE: British journal of dermatology : (1951), (1998), 139(6), 1026-1032, 39 refs.
ISSN: 0007-0963 CODEN: BJDEAZ
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
AVAILABILITY: INIST-1043, 354000073364160130
ABSTRACT: Hypersensitivity syndrome (HSS) usually refers to severe drug eruption associated with systemic symptoms and eosinophilia. **Interleukin** (**IL**

)-5 regulates **eosinophil** counts with the help of IL- 3 and granulocyte-macrophage colony-stimulating factor (GM-CSF). Blood **IL-5** levels have been reported to be increased in patients with eosinophilia secondary to parasitic infections or idiopathic eosinophilia. but have never been **evaluated** in **drug**-induced eosinophilia. The aim of our study was to determine whether **IL-5**, IL- 3 and GM-CSF are involved in eosinophilia in patients with drug-induced HSS. Plasma levels of IL-3, **IL-5** and GM-CSF were assayed by ELISA in seven patients with drug-induced HSS, in eight patients with cutaneous adverse drug reactions not associated with eosinophilia, and in five patients with eosinophilia unrelated to drug treatment. **IL-5** levels were normal in all eight patients with drug eruptions without eosinophilia, and increased in five of the seven patients with HSS. In the latter patients, **IL-5** levels peaked several days before highest **eosinophil** counts were noted, and returned to normal within a few days, even when eosinophilia persisted. In patients with eosinophilia unrelated to drug treatment. **IL-5** levels, although significantly increased, remained lower than in HSS patients. IL- 3 and GM-CSF could not be detected in any group, at any time. Our results show that **IL-5** is involved in drug-related eosinophilia. As **IL-5** production was only involved in the early stages of the reaction, it is suggested that **IL-5** mainly derives from activated lymphocytes rather than **eosinophils.** Our results support the clinical relevance of previous in **vitro** findings. Further studies are needed to test whether assays of **IL-5** production by lymphocytes of patients stimulated by the suspected drug and/or its metabolites, are useful in establishing causality in drug-induced reactions associated with eosinophilia.

CLASSIFICATION CODE: 002B02U10; Life sciences; Medical sciences; Pharmacology; Toxicology

CONTROLLED TERM: Toxicity; Drug; **Interleukin** 3; **Interleukin** 5; Granulocyte macrophage colony stimulating factor; Human; Hypersensitivity syndrome

BROADER TERM: Immunopathology; **Cytokine**

L115 ANSWER 33 OF 42 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2005-07242 BIOTECHDS
TITLE: New isolated nucleic acid molecules and encoded IL-17 A/F polypeptides useful for diagnosing or treating degenerative cartilaginous disorders and other immune diseases (e.g. inflammation, rheumatoid arthritis or diabetes); involving vector-mediated gene transfer and expression in Chinese hamster ovary, Escherichia coli, yeast and baculo virus infected insect cell for use in diagnosis, therapy and gene therapy
AUTHOR: ARNOTT D; GURNEY A; HASS P; LEE J; WU Y
PATENT ASSIGNEE: GENENTECH INC
PATENT INFO: WO 2005010044 3 Feb 2005

APPLICATION INFO: WO 2004-US17581 2 Jun 2004
PRIORITY INFO: US 2003-486457 11 Jul 2003; US 2003-485599 8 Jul 2003
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2005-123127 [13]
ABSTRACT: DERWENT ABSTRACT:
NOVELTY - An isolated nucleic acid molecule for treating degenerative cartilaginous disorders and other inflammatory diseases, is new.

DETAILED DESCRIPTION - A nucleic acid molecule comprises: (a) a nucleotide sequence encoding an **Interleukin**-17A/F polypeptide comprising a sequence of 155 or 163 amino acids fully defined in the specification (SEQ ID NOS: 3 and 4, respectively), with or lacking its associated signal peptides; (b) a nucleotide sequence comprising 1859 or 559 bp fully defined in the specification (SEQ ID NOS: 5 and 6, respectively); (c) a nucleotide sequence comprising the full-length coding sequence of SEQ ID NO: 5 and 6; or (d) a nucleotide sequence having at least 80% nucleic acid identity to any of (a)-(c). INDEPENDENT CLAIMS are also included for the following: (1) a vector comprising the above nucleic acid molecule; (2) a host cell comprising the vector; (3) a process for producing an IL-17 A/F polypeptide or an IL-17 A/F polypeptide complex comprising SEQ ID NOS: 3 and 4, or an antibody; (4) an isolated polypeptide comprising: (a) the amino acid sequence of an IL-17A/F polypeptide comprising SEQ ID NOS: 3 and 4, with or lacking its associated signal peptides; or (b) an amino acid sequence at least 80% identical to (a); (5) a chimeric molecule comprising the above polypeptide fused to a heterologous amino acid sequence; (6) a composition of matter comprising the IL-17A/F polypeptide, an agonist or antagonist of the IL-17A/F polypeptide, or an antibody that specifically binds to the IL-17A/F polypeptide, in combination with a carrier; (7) an isolated antibody which specifically binds to the above polypeptide; (8) an article of manufacture comprising a container, a label on the container, and the above composition of matter contained within the container, where label on the container indicates that the composition of matter can be used for treating an immune related disease; (9) methods of treating or diagnosing an immune related disorder in a mammal; (10) a method for determining the presence of an IL-17A/F polypeptide in a sample suspected of containing the polypeptide; (11) methods of identifying a compound that inhibits the activity of the IL-17 A/F polypeptide, that inhibits the expression of a gene encoding the IL-17 A/F polypeptide, or that mimics the activity of the IL-17A/F polypeptide; (12) methods of stimulating or inhibiting the proliferation of T-lymphocytes; (13) methods of enhancing or decreasing the infiltration of inflammatory cells into a tissue of a mammal; and (14) a method of making an IL-17A/F polypeptide complex comprising SEQ ID NOS: 3 and 4.

BIOTECHNOLOGY - Preferred Nucleic Acid: The nucleic acid molecule alternatively has at least 85-99% nucleic acid sequence identity to the above-mentioned nucleotide sequences. Alternatively, the nucleic acid molecule comprises any of the 34 nucleotide sequences as mentioned in the specification (SEQ ID NOS: 43-76), and encodes a Fab fragment capable of binding to IL-17 A/F. Preferred Polypeptide: The

IL-17A/F polypeptide comprises a covalently linked heterodimeric complex comprising SEQ ID NOS: 3 and 4. The heterodimeric complex comprises 2 interchain disulfide linkages between SEQ ID NOS: 3 and 4. The polypeptide alternatively comprises at least 85-99% amino acid sequence identity to the above-mentioned amino acid sequences. Preferred Chimeric Molecule: The heterologous amino acid sequence is an epitope tag sequence or an Fc region of an immunoglobulin. Preferred Vector: The vector is operably linked to control sequences recognized by a host cell transformed with the vector. Preferred Host Cell: The host cell is a CHO cell, an Escherichia coli cell, a yeast cell or a Baculovirus infected insect cell. Preferred Antibody: The antibody is an antibody fragment, a monoclonal antibody, a humanized antibody, a single-chain antibody or an anti-idiotypic antibody. The monoclonal antibody preferably has nonhuman complementarity determining region (CDR) residues and human framework region (FR) residues. The antibody is labeled and is immobilized on a solid support. The antibody fragment or single-chain antibody comprises a Fab fragment selected from any of the 34 amino acid sequences (e.g. 89, 94 or 101 amino acids) fully defined in the specification (SEQ ID NOS: 9-42), and where the Fab fragment further comprises one or more heavy chain variable regions containing CDR-H1 consisting of amino acid residues 7-16 of SEQ ID NOS: 9-42, and/or CDR-H2 consisting of amino acid residues 30-46 of SEQ ID NOS: 9-42, and/or CDR-H3 consisting of amino acid residues 78-96 of SEQ ID NOS: 9-42, where the isolated Fab fragment is capable of binding IL-17 A/F. The CDR-H1 region of SEQ ID NOS: 9-42 comprises at least amino acid residues 7-10 corresponding to the amino sequence of SEQ ID NO: 77, which is capable of binding IL-17 A/F. The CDR-H2 region comprises at least amino acid residues 41-46 corresponding to amino acid sequence of SEQ ID NO: 78, which is capable of binding IL-17A/F. The antibody is an anti-IL-17A/F agonist or antagonist antibody. Preferred Composition: The carrier is a pharmaceutical carrier. The IL-17A/F polypeptide, agonist or antagonist of the IL-17A/F polypeptide, or the antibody is capable of increasing or inhibiting the proliferation of T-lymphocytes in a mammal, or increasing or decreasing infiltration of inflammatory cells into a tissue of a mammal. The composition comprises a therapeutic amount of the IL-17A/F polypeptide, agonist or antagonist of the polypeptide, or the antibody. Preferred Method: Producing the IL-17 A/F polypeptide comprises **culturing** the host cell under conditions for expression of the IL-17A/F polypeptide, and recovering the polypeptide from the cell **culture.** Making the IL-17A/F polypeptide complex comprises co-transfecting host cells with equal amounts of cDNA expression vectors encoding the human IL-17 polypeptide as mentioned above, **culturing** the host cells under conditions for expression of the IL- 17A/F polypeptide complex, and recovering the IL-17A/F polypeptide complex from the cell **culture.** Producing the antibody comprises **culturing** the above host cell under conditions for expression of the antibody, and recovering the antibody from the cell **culture.** Treating an immune related disorder in a mammal comprises administering to the mammal a therapeutic amount of the above polypeptide, agonist or

antagonist of the polypeptide, or the antibody. The immune related disorder is systemic lupus erythematosus, rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, a spondyloarthropathy, systemic sclerosis, an idiopathic inflammatory myopathy, Sjogren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia, autoimmune thrombocytopenia, thyroiditis, diabetes mellitus, immune-mediated renal disease, a demyelinating disease of the central or peripheral nervous system, idiopathic demyelinating polyneuropathy, Guillain-Barre syndrome, a chronic inflammatory demyelinating polyneuropathy, a hepatobiliary disease, infectious or autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, sclerosing cholangitis, inflammatory bowel disease, gluten-sensitive enteropathy, Whipple's disease, an autoimmune or immune-mediated skin disease, a bullous skin disease, erythema multiforme, contact dermatitis, psoriasis, an allergic disease, asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity, urticaria, an immunologic disease of the lung, eosinophilic pneumonia, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, a transplantation associated disease, graft rejection or graft-versus-host-disease. Determining the presence of the IL-17A/F polypeptide in a sample suspected of containing the polypeptide comprises exposing the sample to the anti-IL-17A/F antibody and determining binding of the antibody to a component of the sample. Diagnosing an immune related disease in a mammal comprises detecting the level of expression of a gene encoding the IL-17A/F polypeptide in a test sample of tissue cells obtained from the mammal, and in a control sample of known normal tissue cells of the same cell type, where a higher or lower level of expression of the gene in the test sample as compared to the control sample is indicative of the presence of an immune related disease in the mammal from which the test tissue cells were obtained. Alternatively, diagnosing an immune related disease in a mammal comprises contacting an anti-IL-17 A/F antibody with a test sample of tissue cells obtained from the mammal and detecting the formation of a complex between the antibody and the polypeptide in the test sample, where formation of the complex is indicative of the presence of an immune related disease in the mammal from which the test tissue cells were obtained. Identifying a compound that inhibits the activity of the IL-17 A/F polypeptide comprises contacting cells which normally respond to the polypeptide with the above polypeptide and a candidate compound, and determining the lack of responsiveness by the cell to the polypeptide cited above. Identifying a compound that inhibits the expression of a gene encoding an IL-17 A/F polypeptide comprises contacting cells which normally express the polypeptide with a candidate compound, and determining the lack of expression of the gene. The candidate compound is an antisense nucleic acid. Identifying a compound that mimics the activity of the IL-17A/F polypeptide comprises contacting cells which normally respond to the polypeptide with a candidate compound, and determining the responsiveness by the cell to the candidate compound. Stimulating the proliferation of T-lymphocytes comprises contacting T-lymphocytes with an amount of the IL-17A/F polypeptide or its agonist, where the proliferation of T-lymphocytes is stimulated. Inhibiting the

proliferation of T-lymphocytes comprises contacting T-lymphocytes with an amount of an antagonist of the IL-17A/F polypeptide, where the proliferation of T-lymphocytes is inhibited. Enhancing the infiltration of inflammatory cells into a tissue of a mammal comprises administering to the mammal an amount of the IL-17 A/F polypeptide or its agonist, where the infiltration is enhanced. Decreasing the infiltration of inflammatory cells into a tissue of a mammal comprises administering to the mammal an amount of an antagonist of the above IL-17A/F polypeptide, where the infiltration is decreased. The inflammatory cells are mononuclear cells, **eosinophils** or polymorphonuclear neutrophils (PMNs).

ACTIVITY - Immunosuppressive; Dermatological; Antiinflammatory; Antirheumatic; Antiarthritic; Antithyroid; Antidiabetic; Nephrotropic; Neuroprotective; Nootropic; Hepatotropic; Gastrointestinal-Gen.; Antipsoriatic; Antiallergic; Antiasthmatic. No biological data given.

MECHANISM OF ACTION - Gene therapy.

USE - The composition and methods are useful for diagnosing and treating degenerative cartilaginous disorders and other immune related disorders such as systemic lupus erythematosus, rheumatoid arthritis, thyroiditis, diabetes mellitus, immune-mediated renal disease, a demyelinating disease of the central or peripheral nervous system, a hepatobiliary disease, inflammatory bowel disease, psoriasis, an allergic disease, asthma, eosinophilic pneumonia, graft rejection or graft-versus-host-disease. These may also be used in **drug screening** purposes.

ADMINISTRATION - Dosages may range from about 10 ng/kg-100 mg/kg (preferably 1 microg/kg-10 mg/kg) per day. Administration can be intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial, intralesional, topical, or by sustained-release systems.

EXAMPLE - No relevant example given. (154 pages)

CLASSIFICATION: THERAPEUTICS, Protein Therapeutics; GENETIC TECHNIQUES and APPLICATIONS, Gene Expression Techniques and Analysis; DISEASE, Blood and Hematopoietic Cells; DISEASE, Central Nervous System; DISEASE, Endocrine/Metabolic System; DISEASE, Respiratory System; DISEASE, Kidney; DISEASE, Autoimmune Disease; DISEASE, Other Diseases; BIOMANUFACTURING and BIOCATALYSIS, Animal/Plant Cell Culture; PHARMACEUTICALS, Antibodies; THERAPEUTICS, Gene Therapy; DIAGNOSTICS, Molecular Diagnostics

CONTROLLED TERMS: RECOMBINANT **INTERLEUKIN**-17 PROTEIN PREP., ISOL., VECTOR-MEDIATED GENE TRANSFER, EXPRESSION IN CHO, ESCHERICHIA COLI, YEAST, BACULO VIRUS INFECTED INSECT CELL, MONOCLONAL ANTIBODY, HUMANIZED ANTIBODY, AGONIST, ANTAGONIST, APPL., DEGENERATIVE CARTILAGINOUS DISORDER, IMMUNE-RELATED DISORDER, SYSTEMIC LUPUS ERYTHEMATOSUS, RHEUMATOID ARTHRITIS, THYROIDITIS, DIABETES MELLITUS, IMMUNE-MEDIATED KIDNEY DISEASE, DEMYELINATING DISEASE, CENTRAL NERVOUS SYSTEM DISORDER, HEPATOBILIARY DISEASE, INFLAMMATORY BOWEL DISEASE, PSORIASIS, ALLERGIC DISEASE, ASTHMA, EOSINOPHILIC PNEUMONIA DIAGNOSIS, THERAPY, GENE THERAPY **CYTOKINE** PROTEIN ANTIBODY ENGINEERING CHINESE HAMSTER OVARY ANIMAL MAMMAL BACTERIUM ARTHROPOD IMMUNOSUPPRESSIVE DERMATOLOGICAL ANTIINFLAMMATORY ANTIRHEUMATIC ANTITHYROID ANTIDIABETIC NEPHROTROPIC NEUROPROTECTIVE NOOTROPIC HEPATOTROPIC ANTIPSORIATIC ANTIALLERGIC ANTIASTHMATIC DNA SEQUENCE PROTEIN

SEQUENCE (24, 11)

L115 ANSWER 34 OF 42 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2004-07684 BIOTECHDS
TITLE: Diagnosing an allergy, e.g. atopic dermatitis, comprises measuring expression level of TR3 orphan receptor and transcriptionally inducible nuclear receptor in **eosinophils**;
protein expression level measurement and animalmodel for use in disease therapy
AUTHOR: HASHIDA R; KAGAYA S; SUGITA Y; SAITO H
PATENT ASSIGNEE: GENOX RES INC; JAPAN GEN AGENCY NATION
PATENT INFO: WO 2004005509 15 Jan 2004
APPLICATION INFO: WO 2003-JP8200 27 Jun 2003
PRIORITY INFO: JP 2002-193841 2 Jul 2002; JP 2002-193841 2 Jul 2002
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
OTHER SOURCE: WPI: 2004-122601 [12]
ABSTRACT: DERWENT ABSTRACT:
NOVELTY - Diagnosing an allergy comprising measuring the level of TR3 orphan receptor or TINUR (transcriptionally inducible nuclear receptor) protein or the level of expression of their genes in **eosinophils** of allergy sufferers, and comparing them to the levels found in healthy **eosinophils**, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) a reagent for diagnosing allergy; (2) detecting the effect of compounds on the expression levels of these genes; (3) **screening** for **compounds** that may be used to treat allergies; (4) treatment for allergies containing ligand for TR3 or TINUR receptor; (5) transgenic knock out animal model for allergy; (6) inducing apoptosis in cells by activating the TR3 or TINUR receptor protein; and (7) agent for inducing expression of TR3 and TINUR containing **eosinophil** CD30 receptor ligand.

ACTIVITY - Antiallergic; Dermatological. No biological data given.

MECHANISM OF ACTION - None given.

USE - The method is used for treatment and diagnosis of allergies, preferably atopic dermatitis; and for screening for treatments for allergies (claimed).

EXAMPLE - In **vitro** analysis of the stimulation required for orphan receptor TR3 and TINUR (transcriptionally inducible nuclear receptor) expression in **eosinophils** was investigated by **culturing** healthy **eosinophils** and stimulating them with **cytokines** such as **IL-5** (**interleukin**-5) and IL-4 (**interleukin**-4). However no TR3 induction was observed. However, when apoptosis was induced by anti-CD30 antibodies, TR3 and TINUR were induced within 1-3 hours. Anti-Fax antibody did cause apoptosis but did not induce TR3 or TINUR. This specific pathway leading to **eosinophil** cell death was not limited to asthma, but indicated that it should be useful in the treatment of various other allergies including atopic dermatitis. (158 pages)
CLASSIFICATION: THERAPEUTICS, Protein Therapeutics; GENETIC TECHNIQUES and APPLICATIONS, Gene Expression Techniques and Analysis; GENETIC TECHNIQUES and APPLICATIONS, Transgenic Animals and Animal Models; DISEASE, Other Diseases; DIAGNOSTICS,

Molecular Diagnostics
CONTROLLED TERMS: TR3 ORPHAN RECEPTOR, TRANSCRIPTIONALLY INDUCIBLE NUCLEAR RECEPTOR PROTEIN EXPRESSION LEVEL MEASUREMENT, KNOCKOUT TRANSGENIC ANIMAL, APPL. **DRUG SCREENING**, ALLERGY, ATOPIC DERMATITIS DIAGNOSIS, THERAPY ANTIALLERGIC (23, 15)

L115 ANSWER 35 OF 42 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2004-14394 BIOTECHDS
TITLE: Novel single or multiple target oligonucleotide anti-sense to e.g. initiation codon, intron of respiratory disease-relevant gene e.g. CCR1, RANTES, MCP4, useful for prophylaxis or treating respiratory disease e.g. asthma;
antisense oligonucleotide transfer and expression in host cell for gene therapy
AUTHOR: NYCE J W; SANDRASAGRA A; TANG L; AGUILAR D; MILLER S; SHAHABUDDIN S; LU H; CONG H
PATENT ASSIGNEE: NYCE J W; SANDRASAGRA A; TANG L; AGUILAR D; MILLER S; SHAHABUDDIN S; LU H; CONG H
PATENT INFO: US 2004049022 11 Mar 2004
APPLICATION INFO: US 2003-627930 25 Jul 2003
PRIORITY INFO: US 2003-627930 25 Jul 2003; WO 2002-13135 23 Apr 2002
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2004-293804 [27]
ABSTRACT: DERWENT ABSTRACT:
NOVELTY - An oligonucleotide (oligo) (I) anti-sense to the initiation codon, coding region, 5', or 3' intron-exon junction, intron, region with 2-10 nucleotides of 5'-end and 3'-end of nucleic acid target comprising gene(s) chosen from e.g. **interleukin** (IL)-4 receptor, MCP4 or anti-sense to their corresponding mRNAs, or salts of (I) and optionally surfactant operatively linked to (I), is new.

DETAILED DESCRIPTION - An oligonucleotide (oligo) (I) that is anti-sense to an initiation codon, a coding region, a 5', or 3' intron-exon junction, an intron, a region with 2-10 nucleotides of the 5'-end and the 3'-end or a border section between a coding and non-coding region of a nucleic acid target comprising a gene(s) chosen from **interleukin** -4 receptor, **interleukin**-5 receptor, CCR1, CCR3, Eotaxin-1, RANTES, MCP4, CD23, ICAM, VCAM, tryptase a, tryptase b, PDE4 A, PDE4 B, PDE4 C or PDE4 D gene, or anti-sense to their corresponding mRNAs, or salts of (I), and optionally a surfactant that may be operatively linked to (I). INDEPENDENT CLAIMS are included for: (1) a composition (II) comprising (I) and carrier or diluent and optionally therapeutic agent; (2) a formulation (III) comprising (II), and a hydrophobic carrier; (3) a capusle or cartridge (IV), comprising (III); (4) a vector (V), comprising (I); (5) a cell (VI) comprising (I); (6) a diagnostic or therapeutic kit (VII) for delivery of an oligonucleotide(s) comprising, in separate containers, a delivery device, (II) and instructions for loading (III) into the device and for its use; and (7) screening (M1) a candidate compound for the prevention and/or treatment of a respiratory or lung disease that binds to one or more nucleic acid target(s) or expressed product(s).

BIOTECHNOLOGY - Preferred Oligonucleotide: (I) is anti-sense to 2499 sequences e.g. CTC-CAC-TCA-CTC-CAG-GTG, CTC-CAC-TCA-CTC-CAG, GCA-GCT-GCC-CCA-TGC-TG, GAG-AAG-GCC-TTG-TAA-CC, GCG-CCC-CTG-CTC-CAT-TCG-CC,

TTT-CTT-CCA-GCT-CTG-TGT, CAC-CAC-GCC-CGG-CTT-CTG-TGT, TCT-GCC-CGC-CTC-AGC-CTC-T, GGC-ACC-AGG-CTG-GTC-TCG, TGG-GAG-ATG-CCA-AGG-CAC, GCA-AAG-CCA-CCC-CAT-TGG, GTT-CCC-AGA-GCT-TGC-CAC-CT. (I) is anti-sense to two or more genes or RNAs. In (I), one or more mononucleotide is substituted or modified by one or more of phosphorothioate, chiral phosphorothioate, phosphorodithioate, phosphotriester, aminoalkylphosphotriester, methyl phosphonate, 3'-alkylene phosphonate, chiral phosphonate, phosphinate, phosphoramidate, 3'-amino phosphoramidate, aminoalkylphosphoramidate, thionophosphoramidate, thionoalkylphosphonate, thinoalkylphosphotriester, boranophosphate, morpholino, siloxane, sulfide, sulfoxide, sulfone, formacetyl, thioformacetyl, methylene formacetyl, alkene, sulfamate, methyleneimino, methylenehydrazino, sulfonate, sulfonamide, amide, thioether, carbonate, carbamate, sulfate, sulfite, hydroxylamine, methylene(methyimino), methyleneoxy (methylimino), 2'-O-methyl, or phosphoramidate residues, or their combinations, where all mononucleotides are preferably substituted or modified. In (I), one or more mononucleotide is substituted or modified at the 2' position by one or more of OH, F, O-, S-, N-alkyl, O-alkyl-O-alkyl N-alkenyl, N-alkynyl, O((CH2)n O)m CH3, O(CH2)n OCH3, O(CH2)2 ON(CH3)2, O(CH2)n NH2, O(CH2)n CH3, O(CH2)n ONH2, or O(CH2)n ON((CH2)n CH3))2, where n or m are from 1 to 10, C1 to C10 lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl, O-aralkyl, SH, SCH3, OCN, Cl, Br, CN, CF3, OC3, SOCH3, SO2 CH3, ONO2, NO2, N3, NH2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, poly-alkylamino, or substituted silyl. In (I), one or more mononucleotide is substituted or modified by one or more of 5-methylcytosine (mC), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl adenine, 6-methyl guanine, 2-propyl adenine, 2-propyl guanine, 2-thiouracil, 2-thiothymine, 2-thiocytosine, 5-halouracil, 5-halocytosine, 5-propynyl uracil, 5-propynyl cytosine, 6-azo uracil, 6-azo cytosine, 6-azo thymine, 5-uracil (pseudouracil), 4-thiouracil adenine, 8-halo adenine, 8-amino adenine, 8-thiol adenine, 8-thioalkyl adenine, 8-hydroxyl adenine, 8-halo guanine, 8-amino guanine, 8-thiol guanine, 8-thioalkyl guanine, 8-hydroxyl guanine, 5-bromo uracil, 5-trifuloromethyl uracil, 5-bromo cytosine, 5-trifluoromethyl cytosine, 7-methylguanine, 7-methyladenine, 8-azaguanine, 8-azaadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, 3-deazaadenine, 2-aminopropyladenine, 5-propylnyluracil, 5-propynylcytosine or 5-methylcytosine. The methylated cytosine (mC) is substituted for an unmethylated cytosine (C) in one or more CpG dinucleotide if present in (I). If (I) contains adenosine (A), one or more A is substituted by a universal base chosen from heteroaromatic bases that bind to a thymidine base but having antagonist activity or less than about 0.3 of the adenosine base agonist activity at the adenosine A1, A2b or A3 receptors, or heteroaromatic bases that have no activity or have agonist activity at the adenosine A2a receptor. Substantially all A's are substituted by a universal base(s). The heteroaromatic bases are chosen from pyrimidines or purines that may be substituted by O, halo, NH2, SH, SO, SO2, SO3 COOH, or branched or fused primary or secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl,

alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkenylaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, or arylcycloalkl, which may be further substituted by O, halo, NH2, primary, secondary or tertiary amine, SH, SO, SO2, SO3, cycloalkyl, heterocycloalkyl or heteroaryl. The pyrimidines are substituted at a 1, 2, 3, and/or 4 position, and the purines are substituted at a 1, 2, 3, 4, 7 and/or 8 position. The pyrimidines or purines are chosen from theophylline, caffeine, dyphylline, etophylline, piperazine, bamifylline, enprofylline or xanthine. The universal base is chosen from 3-nitropyrrole-2'-deoxynucleoside, 5-nitroindole, 2-deoxyribosyl-(5-nitroindole), 2-deoxyribofuranosyl-(5-nitroindole), 2'-deoxyinosine, 2'-deoxynebularine, 6H, 8H-3, 4-dihydropyrimido (4,5-c) oxazine-7-one or 2-amino-6-methoxyaminopurine. (I) consists of up to 10%, preferably 5 or 3 % A. (I) is more preferably free of A. The nucleic acid is linked to an agent that enhances cell internalization or up-take and/or a cell targeting agent. The cell internalization or up-take enhancing agent comprises transferring, asialoglycoprotein or streptavidin. The cell targeting agent comprises a vector, and the nucleic acid is operatively linked to the vector. The vector comprises a prokaryotic or eukaryotic vector. Preferred Composition: In (II), the carrier or diluent comprises gaseous, liquid or solid carrier or diluent. The therapeutic agents comprise surfactants, antioxidants, flavoring and coloring agents, filler, volatile oils, buffering agents, dispersants, RNA inactivating agents, antioxidants, flavoring agents, propellants or preservatives. The surfactants are lipid or non-lipid surfactants. The surfactants comprises surfactant protein A, surfactant protein B, surfactant protein C, surfactant protein D, surfactant protein E, its active fragments, non-dipalmitoyl disaturated phosphatidylcholine, dipalmitoylphosphatidylcholine, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, ubiquinones, lysophosphatidylethanolamine, lysophosphatidylcholine, palmitoyl-lysophosphatidylcholine, dehydroepiandrosterone, dolichols, sulfatidic acid, glycerol-3-phosphate, dihydroxyacetone phosphate, glycerol, glycero-3-phosphocholine, dihydroxyacetone, palmitate, cytidine diphosphate (CDP) diacylglycerol, CDP choline, choline, choline phosphate, artificial lamellar bodies vehicles for surfactant components, OMEGA-3 fatty acids, polyenic acid, polyenoic acid, lecithin, palmitic acid, non-ionic ethylene and/or propylene oxide block copolymers, polyoxypropylene, polyoxyethylene, poly(vinyl amine) with dextran and/or alkanoyl side chains, polyoxy ethylene 23 lauryl ether (Brij 35 (RTM)), t-octyl phenoxy polyethoxy ethanol (Triton X-100 (RTM)), dipalmitoyl phosphatidyl choline (DPPC), phosphatidyl glycerol (PG) (ALEC (RTM)), tyloxapol (Exosurf (RTM)), surfactant-associated proteins (Survanta (RTM))or C22H19C10 (Atovaquone (RTM)). The RNA inactivating agent comprises an enzyme. The enzyme is a ribozyme. (I) further comprises propellant. (I) is present in an amount of 0.01-99.99 w/w of (II). Preferred Formulation: (III) is chosen from intrabuccal, intrapulmonary, respirable,

nasal, inhalable, intracavitary, intraorgan, or slow release formulations. The carrier is chosen from a solid or liquid carrier. (III) comprises a sprayable or aerosolizable powder, solution, suspension or emulsion, aqueous or alcoholic solution or oily solution or suspension, or oil-in-water or water-in-oil emulsion. (III) comprises a formulation of particle size 0.5-10 mu, or 10-500 mu. (III) preferably comprises a nasal formulation of particle size 10-500 mu. (III) is a respirable or inhalable formulation comprising a solid powdered or liquid aerosol or spray of particle size 0.5-10 mu. (III) is given in bulk or in single or multiple unit dose form. Preferred Kit: In (VII) delivery device comprises a nebulizer, a dry powder inhaler, a pressurized inhaler or insufflator. The delivery device delivers single metered doses. The delivery device is adapted for receiving and piercing or opening a capsule(s), blister(s), or cartridge(s) and producing a solid powdered or liquid aerosol or spray. In (VII), (II) is in an inhalable, respirable, nasal, intracavitary, intraorgan or intrapulmonary formulation. (II) has particle size 0.5-10 mu or preferably 10-500 mu. (II) is provided in a pierceable or openable capsule, blister or cartridge. (III) comprises the delivery device, a surfactant, (II) and other therapeutic agents. (VII) further comprises a solvent chosen from organic solvents or organic solvents mixed with one or more co-solvents. Preferred Method: In (M1), the nucleic acid target(s) or their expressed product(s) is (are) in a purified form from the expression system. The expressed product(s) is (are) expressed in or on the cell. The binding is detected by a label. The candidate compound suppresses the expression of one or more nucleic acid target(s). (M1) further involves step of contacting a candidate compound with or introducing into a cell expressing the one or more nucleic acid target(s) or their expressed product(s), and detecting the suppression, reduction or inhibition of their expression. The suppression, reduction or inhibition is detected by measuring the level of the transcribed mRNA of the genes. The cell comprises a construct comprising a nucleic acid target that is linked to a reported gene system in a cell.

ACTIVITY - Antiinflammatory; Antiasthmatic; Antiallergic; Hypotensive. No biological data is given.

MECHANISM OF ACTION - Antisense therapy.

Eosinophils are predominant effector cells in allergic diseases, which were attracted by several CC chemokines into the inflammatory tissue. The human **eosinophils** are recruited by eotaxin, RANTES and MCP-3 and MCP-4 through CCR3. These chemokines were potential therapeutic target for asthma and other allergic diseases. The effect of antisense oligonucleotides (ASODNs) (17-20 bases in length) designed to hybridize to the specific sequence in the 3'- and 5'-untranslated regions as well as the coding regions of RANTES and MCP-4 mRNA, in the inhibition of mRNA and protein expression in BEAS-2B human airway epithelial cells was studied as follows. Confluent monolayers of BEAS-2B cells were either treated with **culture** medium, or transfected with RANTES specific antisense e.g. ATTTTTCATGTTTGCCAGTA, or MCP-4 specific antisense e.g. TCTGGCTGAGCAAGTCCCTG, or Wobble, a control ASODN (5 microg/ml), in the presence of lipofectin (10 microg/ml), a carrier lipid, for 4 hours followed by a 4

hours (for mRNA expression) or 18 hours (for protein expression) treatment with the complete medium. mRNA expression was determined by TaqMan using a specific MCP-4 or RANTES probe. 43 % of ASODNs specific to MCP-4 and 32 % of RANTES ASODNs showed more than 50 % inhibition of MCP-4 and RANTES mRNA expression respectively. The level of MCP-4 or RANTES protein in the conditioned medium of the BEEAS-2B cells, either untransfected with specific or control ASODNs was determined by enzyme linked immunosorbent assay (ELISA). The results showed undetectable levels of MCP-4 and low levels of RANTES expression in BEAS-2B cells treated with medium only. Treatment of BEAS-2B cells with tumor necrosis factor (TNF)-alpha and interferon (IFN)-gamma induced the levels of both chemokines. Treatment of BEAS-2B cells with antisense prior to **cytokine** treatment, inhibited protein expression. 8 % of MCP-4 ASODNs and 15 % of RANTES ASODNs inhibited greater than 25 % and 50 % of MCP-4 and RANTES protein expression respectively. These findings suggested that ASODNs effectively inhibited RANTES and MCP-4 expression.

USE - (I) is useful for reducing or inhibiting expression of a gene or mRNA encoding **interleukin**-4 receptor, **interleukin**-5 receptor, CCR1, CCR3, Eotaxin-1, RANTES, MCP4, CD23, ICAM, VCAM, tryptase a, tryptase b, PDE4 A, PDE4 B, PDE4 C, or PDE4 D. (II) is useful for preventing or treating a respiratory or lung disease. The respiratory or lung disease is associated with hyperresponsiveness to and/or increased levels of, adenosine and/or levels of adenosine (A) receptor(s), and/or asthma and/or lung allergy(ies) associated with inflammation or an inflammatory disease. The subject is a mammal. The mammal is a human or a non-human mammal. (I) is useful for production of a medicament for the prevention and/or treatment of a respiratory or lung disease. The respiratory or lung disease is chosen from airway inflammation, allergy(ies), asthma, impeded respiration, cystic fibrosis (CF), chronic obstructive pulmonary diseases (COPD), allergic rhinitis (AR), acute respiratory distress syndrome (ARDS), pulmonary hypertension, lung inflammation, bronchitis, airway obstruction, or bronchoconstriction. (All claimed.)

ADMINISTRATION - (II) is administered intrapulmonary, intraorgan, intracavitarily, intrabuccally, intranasally, by inhalation or into the subject's respiratory system. (II) is administered in an amount of 0.005-150, preferably, 0.01-75, more preferably 1-50 mg/kg (claimed).

EXAMPLE - No relevant example is given. (174 pages)

CLASSIFICATION: THERAPEUTICS, Gene Therapy; GENETIC TECHNIQUES and APPLICATIONS, Gene Expression Techniques and Analysis; DISEASE, Respiratory System; DIAGNOSTICS, Molecular Diagnostics

CONTROLLED TERMS: VECTOR-MEDIATED **INTERLEUKIN**-4 RECEPTOR, **INTERLEUKIN**-5 RECEPTOR, CCR1, CCR3, EOTAXIN-1, RANTES, MCP4, CD23, ICAM, VCAM, TRYPTASE-A, TRYPTASE-B, PDE4-A, PDE4-B, PDE4-C, PDE4-D SINGLE, MULTIPLE TARGET GENE-, RNA-SPECIFIC ANTISENSE OLIGONUCLEOTIDE TRANSFER, EXPRESSION IN HUMAN **EOSINOPHIL**, RIBOZYME, INITIATION CODON, CODING REGION, 5', 3' INTRON-EXON JUNCTION, INTRON EVALUATION, HYDROPHOBIC CARRIER, CAPUSLE, CARTRIDGE, **DRUG SCREENING**, MONONUCLEOTIDE SUBSTITUTION, MODIFICATION, LIPID, NON-LIPID SURFACTANT,

ANTIOXIDANT, FLAVORING, COLORING AGENT, FILLER, VOLATILE OIL, BUFFERING AGENT, DISPERSANT, RNA INACTIVATING AGENT, FLAVORING AGENT, PROPELLANT, PRESERVATIVE TREATMENT, ELISA, APPL. RESPIRATORY, LUNG DISEASE, ASTHMA, LUNG ALLERGY, INFLAMMATION, INFLAMMATORY DISEASE, IMPEDED RESPIRATION, CYSTIC FIBROSIS, CHRONIC OBSTRUCTIVE PULMONARY DISEASE, ALLERGIC RHINITIS, ACUTE RESPIRATORY DISTRESS SYNDROME, PULMONARY HYPERTENSION, LUNG INFLAMMATION, BRONCHITIS, AIRWAY OBSTRUCTION, BRONCHOCONSTRICTION THERAPY, DIAGNOSIS, GENE THERAPY RNA ENZYME ANALYSIS IMMUNOASSAY DNA SEQUENCE (23, 30)

L115 ANSWER 36 OF 42 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2004-12751 BIOTECHDS
TITLE: New isolated IL-17 nucleic acids and polypeptides, useful for diagnosing and treating disorders associated with aberrant expression or activity of the IL-17 polypeptide, such as degenerative cartilaginous and immune-related disorders; vector-mediated PRO protein gene transfer and expression in host cell for recombinant protein production, **drug screening** and gene therapy
AUTHOR: CHEN J; FILVAROFF E; FONG S; GODDARD A; GODOWSKI P; GRIMALDI C; GURNEY A; LI H; HILLAN K; TUMAS D; VANLOOKEREN M; VANDLEN R; WATANABE C K; WILLIAMS P M; WOOD W I; YANSURA D
PATENT ASSIGNEE: GENENTECH INC
PATENT INFO: US 2004043397 4 Mar 2004
APPLICATION INFO: US 2003-408385 7 Apr 2003
PRIORITY INFO: US 2003-408385 7 Apr 2003; US 2000-175481 11 Jan 2000
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2004-225695 [21]
ABSTRACT: DERWENT ABSTRACT:
NOVELTY - An isolated nucleic acid (I) is new.

DETAILED DESCRIPTION - An isolated nucleic acid is at least 80% identity to a nucleotide sequence encoding a polypeptide or an extracellular domain of a polypeptide with any of 8 fully defined sequences of 180-705 amino acids (SEQ ID NO: 2, 4, 6, 8, 12, 14, 16 or 18) as given in the specification, lacking or with its associated signal peptide, and has any of 8 fully defined sequences or full-length coding sequences of 687-2380 bp (SEQ ID NO: 1, 3, 5, 7, 11, 13, 15 or 17) as given specification, or has DNA deposited under ATCC accession number 209866, 203552, PTA-1185, PTA-2108, PTA202, PTA-1535, PTA-1082 or PTA-2591.INDEPENDENT CLAIMS are also included for: (1) a vector comprising (I); (2) a host cell comprising the vector of (1); (3) producing a PRO polypeptide from a **culture** of the host cell of (2); (4) an isolated polypeptide (II) encoded by (I), and having at least 80% sequence identity to SEQ ID NO: 2, 4, 6, 8, 12, 14, 16 or 18; (5) a chimeric molecule comprising (II) fused to a heterologous amino acid sequence; (6) an antibody which specifically binds to (II); (7) a composition comprising (II), an agonist or antagonist of (II), or an antibody of (6), together with a carrier; (8) treating an immune related disorder in a mammal, comprising administering (II), an agonist or antagonist of (II), or an antibody of (6); (9) determining the presence of a PRO1031, PRO1122, PRO10272, PRO21175, PRO20110, PRO5801, PRO20040 or PRO20026 polypeptide in a sample, using an appropriate antibody; (10) diagnosing an immune related disease in a mammal, comprising detecting

the level of expression of a gene encoding PRO1031, PRO1122, PRO10272, PRO21175, PRO20110, PRO5801, PRO20040, PRO9877 or PRO20026 polypeptide in a test sample and comparing the level to that in a control sample; (11) identifying a compound that inhibits or mimics the activity of or the expression of a gene encoding a PRO1031, PRO1122, PRO10272, PRO21175, PRO20110, PRO5801, PRO20040, PRO9877 or PRO20026 polypeptide; (12) stimulating proliferation of T-lymphocytes or enhancing infiltration of inflammatory cells, by contacting T-lymphocytes with or administering (II) or an agonist of (II); (13) inhibiting proliferation of T-lymphocytes or decreasing infiltration of inflammatory cells into a tissue of a mammal, by contacting T-lymphocytes with or administering an antagonist of a PRO1031 or PRO10272 polypeptide; (14) inhibiting angiogenesis induced by a PRO1031 polypeptide or its agonist in a mammal, by administering an anti-PRO1031 antibody or an antagonist of the polypeptide to the mammal; (15) stimulating angiogenesis induced by a PRO1031 polypeptide or its agonist in a mammal, by administering the polypeptide; (16) treating a degenerative cartilaginous disorder in a mammal, by administering a PRO1031, PRO1122, PRO10272 or PRO20110 polypeptide, agonist or antagonist; (17) a kit for use in the treatment of a degenerative cartilaginous disorder comprising a PRO1031, PRO1122 or agonist or antagonist; (18) detecting a polypeptide designated as A, B, or C, or detecting a polypeptide designated as D, E or F in a sample suspected of containing an A, B, or C, or an D, E or F polypeptide, respectively, by contacting the sample with a polypeptide designated as D, E, or F, or A, B or C, respectively, and determining the formation of a A/D, B/D, C/E or C/F polypeptide conjugate in the sample, where A is a PRO1031 polypeptide (IL-17B), B is a PRO10272 polypeptide (IL-17E), C is a PRO20110 polypeptide (IL-17F), D is a PRO5801 polypeptide (IL-17RH1), E is a PRO1 polypeptide (IL-17R), and F is a PRO20040 polypeptide (IL-17RH2); (19) linking a bioactive molecule to a cell expressing a polypeptide designated as A, B, or C, or D, E or F, by contacting the cell with a polypeptide designated as D, E, or F, or A, B or C, respectively, that is bound to the bioactive molecule, and allowing the A, B, or C and the D, E, or F polypeptides to bind to one another, thereby linking the bioactive molecules to the cell, where A is a PRO1031 polypeptide, B is a PRO10272 polypeptide, C is a PRO20110 polypeptide, D is a PRO5801 polypeptide, E is a PRO1 polypeptide, and F is a PRO20040 polypeptide; (20) modulating at least one biological activity of a cell expressing a polypeptide designated as A, B, or C, or D, E or F, by contacting the cell with a polypeptide designated as D, E, or F, or A, B or C, respectively, or an anti-A, anti-B, or anti-C, or an anti-D, anti-E or anti-F polypeptide antibody, respectively, where the polypeptide or antibody binds to the A, B, or C, or D, E or F polypeptide, thereby modulating at least one biological activity of the cell, where A is a PRO1031 polypeptide, B is a PRO10272 polypeptide, C is a PRO20110 polypeptide, D is a PRO5801 polypeptide, E is a PRO1 polypeptide, and F is a PRO20040 polypeptide; and (21) detecting a tumor in a mammal, by detecting overexpression of a PRO polypeptide.

BIOTECHNOLOGY - Preferred Host Cell: The cell is preferably a CHO, Escherichia coli, yeast or insect cell.

Searched by Barb O'Bryen, STIC 2-2518

Preferred Chimeric Molecule: The heterologous amino acid sequence in the chimeric molecule is an epitope tag sequence or an Fc region of an immunoglobulin. Preferred Antibody: The antibody is a monoclonal, humanized or a single-chain antibody. Preferred Method: The candidate compound in the method of (11) is an antisense nucleic acid. The inflammatory cells in the method of (12) or (13) are mononuclear cells, **eosinophils** or polymorphonuclear neutrophils. The sample in the method of (18) comprises cells suspected of expressing the A, B or C, or D, E or F polypeptide. The D, E or F, or A, B or C is preferably labeled with a detectable label, and is attached to a solid support. The bioactive material in the method of (19) is a toxin, a radiolabel or an antibody, and causes the death of the cell. The cell in the method of (20) is killed. The tumor in the method of (21) is a lung, colon or breast tumor.

ACTIVITY - Immunosuppressive; Osteopathic; Antiarthritic; Antirheumatic; Antiinflammatory; Antithyroid; Antidiabetic; Neuroprotective; CNS-Gen.; Virucide; Gastrointestinal-Gen.; Respiratory-Gen.; Hepatotropic; Gastrointestinal; Dermatological; Antiallergic; Antianemic; Hemostatic; Antipsoriatic; Antiasthmatic; Vasotropic; Angiogenesis-Inhibitor / Angiogenesis Stimulator.

MECHANISM OF ACTION - **Interleukin**-17 agonist; **Interleukin**-17 antagonist.

USE - The methods and compositions of the present invention are useful for diagnosing and treating disorders associated with the aberrant expression or activity of a PRO polypeptide. The disorders include a degenerative cartilaginous disorder and immune related diseases, such as systemic lupus erythematosis, rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, spondyloarthropathy, systemic sclerosis, an idiopathic inflammatory myopathy, Sjogren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia, autoimmune thrombocytopenia, thyroiditis, diabetes mellitus, immune-mediated renal disease, a demyelinating disease of the central or peripheral nervous system, idiopathic demyelinating polyneuropathy, Guillain-Barre syndrome, a chronic inflammatory demyelinating polyneuropathy, a hepatobiliary disease, infectious or autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, sclerosing cholangitis, inflammatory bowel disease, gluten-sensitive enteropathy, Whipple's disease, an autoimmune or immune-mediated skin disease, a bullous skin disease, erythema multiforme, contact dermatitis, psoriasis, an allergic disease, asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity, urticaria, an immunologic disease of the lung, eosinophilic pneumonia, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, a transplantation-associated disease, graft rejection or graft-versus-host-disease (claimed).

ADMINISTRATION - Dosage of the pharmaceutical composition ranges from 1-15 mg/kg. Routes of administration include oral, pulmonary, intramuscular, intraperitoneal, intravenous, subcutaneous, inhalation, transdermal, nasal and vaginal.

EXAMPLE - An expressed sequence tag (EST) DNA database was searched and an EST was identified. The EST was Incyte 1347523 also called DNA49665. Based on DNA49665,

oligonucleotides were synthesized. Forward and reverse PCR primers were then used for hybridization, and the library screened to isolate clones encoding the PRO1122 gene. DNA sequencing of the clones isolated gave the full length DNA sequence for PRO1122 with a fully defined sequence of 1046 bp, given in the specification. (146 pages)

CLASSIFICATION: THERAPEUTICS, Protein Therapeutics; GENETIC TECHNIQUES and APPLICATIONS, Gene Expression Techniques and Analysis; GENETIC TECHNIQUES and APPLICATIONS, Genomic Technologies; BIOINFORMATICS and ANALYSIS, Databases; DISEASE, Cancer; BIOMANUFACTURING and BIOCATALYSIS, Animal/Plant Cell Culture; DIAGNOSTICS, Molecular Diagnostics; DIAGNOSTICS, Antibody-Based Diagnostics; THERAPEUTICS, Gene Therapy; DISEASE, Neuromuscular System; DISEASE, Endocrine/Metabolic System; DISEASE, Kidney; DISEASE, Central Nervous System; DISEASE, Respiratory System; DISEASE, Liver

CONTROLLED TERMS: RECOMBINANT **INTERLEUKIN**-17 PREP., VECTOR-MEDIATED PRO PROTEIN GENE TRANSFER, EXPRESSION IN CHO CELL, ESCHERICHIA COLI, YEAST HOST CELL, MOLECULAR WEIGHT MARKER, PROTEIN ELECTROPHORESIS, DNA PROBE, AGONIST, ANTAGONIST, MONOCLONAL ANTIBODY, HUMANIZED ANTIBODY, SINGLE CHAIN ANTIBODY, DNA PRIMER, POLYMERASE CHAIN REACTION, EXPRESSED SEQUENCE TAG DATABASE, AGONIST, ANTAGONIST, APPL. **DRUG SCREENING**, LUNG, COLON, MAMMA CANCER, DEGENERATIVE CARTILAGINOUS DISORDER, IMMUNE-RELATED DISEASE, SYSTEMIC LUPUS ERYTHEMATOSIS, RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, JUVENILE CHRONIC ARTHRITIS, SPONDYLOARTHROPATHY, SYSTEMIC SCLEROSIS, IDIOPATHIC INFLAMMATORY MYOPATHY, SJOGREN SYNDROME, SYSTEMIC VASCULITIS, SARCOIDOSIS, AUTOIMMUNE HEMOLYTIC ANEMIA, AUTOIMMUNE THROMBOCYTOPENIA, THYROIDITIS, DIABETES MELLITUS, IMMUNE-MEDIATED KIDNEY DISEASE, DEMYELINATING DISEASE, CENTRAL, PERIPHERAL NERVOUS SYSTEM DISEASE, IDIOPATHIC DEMYELINATING POLYNEUROPATHY, GUILLAIN-BARRE SYNDROME, CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY, HEPATOBILIARY DISEASE, INFECTIOUS, AUTOIMMUNE CHRONIC ACTIVE HEPATITIS, PRIMARY BILIARY CIRRHOSIS, GRANULOMATOUS HEPATITIS, SCLEROSING CHOLANGITIS, INFLAMMATORY BOWEL DISEASE, GLUTEN-SENSITIVE ENTEROPATHY, WHIPPLE DISEASE, AUTOIMMUNE, IMMUNE-MEDIATED SKIN DISEASE, BULLOUS SKIN DISEASE, ERYTHEMA MULTIFORME, CONTACT DERMATITIS, PSORIASIS, ALLERGIC DISEASE, ASTHMA, ALLERGIC RHINITIS, ATOPIC DERMATITIS, FOOD HYPERSENSITIVITY, URTICARIA, LUNG IMMUNOLOGIC DISEASE, EOSINOPHILIC PNEUMONIA, IDIOPATHIC PULMONARY FIBROSIS, HYPERSENSITIVITY PNEUMONITIS, TRANSPLANTATION-ASSOCIATED DISEASE, GRAFT REJECTION, GRAFT-VERSUS-HOST-DISEASE THERAPY, DIAGNOSIS, GENE THERAPY CYTOKINE PROTEIN LYMPHOKINE CHINESE HAMSTER OVARY CELL CULTURE MAMMAL ANIMAL BACTERIUM FUNGUS HYBRIDIZATION ANTIBODY ENGINEERING DNA AMPLIFICATION BIOINFORMATICS TUMOR DNA SEQUENCE PROTEIN SEQUENCE (23, 26)

L115 ANSWER 37 OF 42 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2004-05717 BIOTECHDS

TITLE: New nucleic acids encoding PRO polypeptides having sequence identity to **Interleukin**-17, useful for diagnosing or treating of immune related diseases e.g. rheumatoid arthritis, thyroiditis, diabetes mellitus or allergic rhinitis;
recombinant protein production and antagonist and agonist

for use in disease therapy and gene therapy

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ABSTRACT: DERWENT ABSTRACT:

NOVELTY - An isolated nucleic acid (I) encoding a PRO polypeptide, is new.

DETAILED DESCRIPTION - An isolated nucleic acid (I) encoding a PRO polypeptide, is new. (I) has at least 80 % identity to: (a) a nucleotide sequence encoding 9 75-1000 residue polypeptide sequences (SEQ ID NO. 2, 4, 6, 8, 10, 12, 14 or 16); (b) a nucleotide sequence encoding (SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16) lacking its associated signal peptide; (c) a nucleotide sequence encoding an extracellular domain of (SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16) with or without its associated signal peptide; (d) 9 750-4000 nucleotide sequences (SEQ ID NO. 1, 3, 5, 7, 9, 11, 13, 15 or 17); or (e) the full length coding sequence of (SEQ ID NO. 1, 3, 5, 7, 9, 11, 13, 15 or 17) or of cDNA deposited under ATCC accession number 209866, 203552, PTA-1185, PTA-2108, PTA-202, PTA-1535, PTA-1082 or PTA-2591. INDEPENDENT CLAIMS are also included for the following: (1) a vector comprising (I); (2) a host cell comprising the vector; (3) a process for producing a PRO polypeptide comprising **culturing** the host cell under conditions suitable for expression of the polypeptide and recovering the polypeptide form the cell **culture**; (4) an isolated polypeptide having at least 80 % identity to: (a) (SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16); (b) (SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16) lacking its associated signal peptide; (c) an extracellular domain of (SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16) with or without its associated signal peptide; or (d) the full-length coding sequence of the cDNA deposited under ATCC accession number 209866, 203552, PTA-1185, PTA-2108, PTA-202, PTA-1535, PTA-1082 or PTA-2591; (5) a chimeric molecule comprising the polypeptide fused to a heterologous amino acid sequence; (6) an antibody which specifically binds to the polypeptide; (7) a composition of matter comprising the polypeptide, an agonist or antagonist of the polypeptide or an antibody that specifically binds to the polypeptide, in combination with a carrier; (8) an article of manufacture comprising a container, a label on the container, and the composition of (7), and where the label on the container indicates that the composition can be used for treating an immune related disease; (9) treating an immune related disorder in a mammal; (10) determining the presence of a PRO1031, PRO1122, PRO10272, PRO21175, PRO20110, PRO5801, PRO20040, PRO9877 or PRO20026 polypeptide in a sample suspected of containing the polypeptide; (11) diagnosing an immune related disease in a mammal; (12) identifying a compound that inhibits the activity of a PRO1031, PRO1122, PRO10272, PRO21175, PRO20110, PRO5801, PRO20040, PRO9877 or PRO20026 polypeptide; (13)

identifying a compound that inhibits the expression of a gene encoding a PRO1031, PRO1122, PRO10272, PRO21175, PRO20110, PRO5801, PRO20040, PRO9877 or PRO20026 polypeptide; (14) identifying a compound that mimics the activity of PRO1031, PRO1122, PRO10272, PRO21175, PRO20110, PRO5801, PRO20040, PRO9877 or PRO20026 polypeptide; (15) stimulating or inhibiting the proliferation of T-lymphocytes; (16) enhancing the infiltration of inflammatory cells into a tissue of a mammal; (17) decreasing the infiltration of inflammatory cells into a tissue of a mammal; (18) inhibiting angiogenesis induced by a PRO1031 polypeptide or an agonist in a mammal; (19) stimulating angiogenesis induced by a PRO1031 polypeptide or an agonist in a mammal; (20) inhibiting angiogenesis in a mammal; (21) treating a degenerative cartilaginous disorder in a mammal;; (22) detecting a PRO polypeptide; (23) linking a bioactive molecule to a cell expressing a PRO; (24) modulating at least one biological activity of a cell expressing a PRO polypeptide; and (25) detecting the presence of a tumor in a mammal.

WIDER DISCLOSURE - (1) identifying agonists of or antagonists to a PRO polypeptide; (2) increasing the activity of T-lymphocytes in a mammal; (3) decreasing the activity of T-lymphocytes in a mammal; and (4) oligonucleotide probes useful for isolating genomic and cDNA nucleotide sequences or as antisense probes.

BIOTECHNOLOGY - Preferred Vector: The vector is operably linked to control sequences recognized by a host cell transformed with the vector. Preferred Host Cell: The cell is a Chinese hamster ovary (CHO) cell, an Escherichia coli cell, a yeast cell or a Baculovirus infected insect cell. Preferred Chimeric Molecule: The chimeric molecule comprises a heterologous amino acid sequence which is an epitope tag sequence or an Fc region of an immunoglobulin. Preferred Antibody: The antibody is a monoclonal antibody, a humanized antibody or a single-chain antibody. Preferred Composition: The composition comprises a pharmaceutical carrier. The composition is also capable of increasing the proliferation of T-lymphocytes in a mammal, inhibiting the proliferation of T-lymphocytes in a mammal, increasing infiltration of inflammatory cells into a tissue of a mammal or decreasing the infiltration of inflammatory cells into a tissue of a mammal. It further comprises an amount of the polypeptide, an agonist or antagonist of the polypeptide or an antibody that specifically binds to the polypeptide. Preferred Method: Treating an immune related disorder in a mammal in need comprising administering to the mammal an amount of the polypeptide, an agonist of the polypeptide, an antagonist of the polypeptide or an antibody that specifically binds to the polypeptide. Determining the presence of a PRO1031, PRO1122, PRO10272, PRO21175, PRO20110, PRO5801, PRO20040, PRO9877 or PRO20026 polypeptide in a sample suspected of containing the polypeptide comprises exposing the sample to an anti-PRO1031, anti-PRO1122, anti- PRO10272, anti-PRO21175, anti-PRO20110, anti-PRO5801, anti-PRO20040, anti-PRO9877 or anti-PRO20026 antibody and determining binding of the antibody to a component of the sample. Diagnosing an immune related disease in a mammal comprises detecting the level of expression of a gene encoding PRO1031, PRO1122, PRO10272, PRO21175, PRO20110, PRO5801, PRO20040, PRO9877 or PRO20026 polypeptide in a test sample of the tissue cells obtained from the mammal and in a

control sample of known normal tissue cells of the same cell type, where a higher or lower level of expression of the gene in the test sample as compared to the control sample is indicative of the presence of an immune related disease in the mammal from which the test tissue cells were obtained. Diagnosing an immune related disease in a mammal comprises contacting an anti-PRO1031, anti-PRO1122, anti- PRO10272, anti-PRO21175, anti-PRO20110, anti-PRO5801, anti-PRO20040, anti-PRO9877 or anti-PRO20026 antibody with a test sample of tissue cells obtained from the mammal and detecting the formation of a complex between the antibody and the polypeptide in the test sample, where formation of the complex is indicative of the presence of an immune related disease in the mammal from which the test tissue cells were obtained. Identifying a compound that inhibits the activity of a PRO1031, PRO1122, PRO10272, PRO21175, PRO20110, PRO5801, PRO20040, PRO9877 or PRO20026 polypeptide comprises contacting the cells which normally respond to the polypeptide with the polypeptide and a candidate compound and determining the lack of responsiveness by the cell to the polypeptide. Identifying a compound that inhibits the expression of agene encoding a PRO1031, PRO1122, PRO10272, PRO21175, PRO20110, PRO5801, PRO20040, PRO9877 or PRO20026 polypeptide comprises contacting the cells which normally express the polypeptide with a candidate compound and determining the lack of expression of the gene. The candidate compound is an antisense nucleic acid. Identifying a compound that mimics the activity of PRO1031, PRO1122, PRO10272, PRO21175, PRO20110, PRO5801, PRO20040, PRO9877 or PRO20026 polypeptide comprises contacting the cells which normally respond to the polypeptide with a candidate compound and determining the responsiveness of the cell to the candidate compound. Stimulating the proliferation of T-lymphocytes comprises contacting T-lymphocytes with an amount of a PRO1031 or PRO10272 polypeptide or an agonist of the PRO1031 or PRO10272 polypeptide, where the proliferation of T-lymphocytes is stimulated. Inhibiting the proliferation of T-lymphocytes comprises contacting T-lymphocytes with an amount of an antagonist of a PRO1031 or PRO10272 polypeptide, where the proliferation of T-lymphocytes is inhibited. Enhancing the infiltration of inflammatory cells into a tissue of a mammal comprises administration to the mammal an amount of a PRO1031 polypeptide or an agonist of the PRO1031 polypeptide, where the infiltration is enhanced. Decreasing the infiltration of inflammatory cells into a tissue of a mammal comprises administration to the mammal an amount of an antagonist of a PRO1031 polypeptide, where the infiltration is decreased. The inflammatory cells are mononuclear cells, **eosinophils** or polymorphonuclear neutrophils (PMNs). Inhibiting angiogenesis induced by a PRO1031 polypeptide or an agonist in a mammal comprises administering an amount of an anti-PRO1031 antibody to the mammal, where angiogenesis is inhibited. Stimulating angiogenesis induced by a PRO1031 polypeptide or an agonist in a mammal comprises administering an amount of the polypeptide to the mammal, where angiogenesis is stimulated. Inhibiting angiogenesis in a mammal comprises administering an amount of an antagonist of a PRO1031 polypeptide to the mammal, where angiogenesis is inhibited. Treating a degenerative cartilaginous disorder in a mammal comprises administering an amount of a PRO1031,

PRO1122, PRO10272 or PRO20110 polypeptide, agonist or antagonist to the mammal suffering from the disorder. Detecting the presence of a tumor in a mammal comprises comparing the level of expression of any PRO polypeptide selected from IL-17, Il-17E or IL-17RH1 in a test sample of cells taken from the mammal and in a control sample of normal cells of the same cell type, where a higher level of expression of the PRO polypeptide in the test sample as compared to the control sample is indicative of the presence of tumor in the mammal. The tumor is lung tumor, colon tumor or breast tumor.

ACTIVITY - Antiallergic; Antiinflammatory; Antiasthmatic; Dermatological; Antianemic; Immunosuppressive; Neuroprotective; Antidiabetic; CNS-Gen.; Gastrointestinal-Gen.; Antiarthritic; Osteopathic; Hepatotropic; Antipsoriatic; Respiratory-Gen.; Antirheumatic; Antithyroid. No biological data given.

MECHANISM OF ACTION - Gene Therapy.

USE - The compositions and methods of the invention are useful for the diagnosis and treatment of immune related diseases in mammal, including humans. The immune related disorder is systemic lupus erythematosis, rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, a spondyloarthropathy, systemic sclerosis, an idiopathic inflammatory myopathy, Sjogren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia, autoimmune thrombocytopenia, thyroiditis, diabetes mellitus, immune-mediated renal disease, a demyelinating disease of the central or peripheral nervous system, idiopathic demyelinating polyneuropathy, Guillain-Barre syndrome, a chronic inflammatory demyelinating polyneuropathy, a hepatobiliary disease, infectious or autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, sclerosing cholangitis, inflammatory bowel disease, gluten-sensitive enteropathy, Whipple's disease, an autoimmune or immune mediated skin disease, a bullous skin disease, erythema multiforme, contact dermatitis, psoriasis, an allergic disease, asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity, urticaria, an immunologic disease of the lung, eosinophilic pneumonia, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, a transplantation associated disease, graft rejection or graft-versus-host disease (all claimed). The nucleic acids encoding PRO polypeptides are used as hybridization probes for gene mapping, generating transgenic animals useful in the development and screening of useful reagents, in chromosome identification or for tissue typing. The PRO polypeptides are also useful in gene therapy, may be employed as molecular weight markers for protein electrophoresis or as therapeutic agents. Anti-PRO antibodies are useful in diagnostic assays or for the affinity purification of PRO for recombinant cell **culture** or natural sources.

ADMINISTRATION - Dosage is 10 ng-100 mg/kg/day, preferably 1 microg-10 mg/kg/day. Administration includes injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial or intralesional routes, topical administration or sustained release system.

EXAMPLE - RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue. The cDNA was primed

with oligo dT containing a NotI site, linked with blunt to SalI hemikinase adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector. DNA sequencing of the clones isolated gave the full-length DNA sequence for PRO1122 and the derived protein PRO1122 sequence. (169 pages)

CLASSIFICATION: THERAPEUTICS, Protein Therapeutics; GENETIC TECHNIQUES and APPLICATIONS, Gene Expression Techniques and Analysis; GENETIC TECHNIQUES and APPLICATIONS, Transgenic Animals and Animal Models; DISEASE, Blood and Hematopoietic Cells; DISEASE, Central Nervous System; DISEASE, Endocrine/Metabolic System; DISEASE, Autoimmune Disease; DISEASE, Infectious Disease (non-viral); DISEASE, Other Diseases; BIOMANUFACTURING and BIOCATALYSIS, Animal/Plant Cell Culture; PHARMACEUTICALS, Antibodies; DIAGNOSTICS, Molecular Diagnostics; THERAPEUTICS, Gene Therapy; DISEASE, Respiratory System

CONTROLLED TERMS: RECOMBINANT PRO PROTEIN, PREP., VECTOR-MEDIATED GENE TRANSFER EXPRESSION IN CHO, ESCHERICHIA COLI, YEAST HOST CELL, MONOCLONAL ANTIBODY, HUMANIZED ANTIBODY, SINGLE CHAIN ANTIBODY, ANTAGONIST, AGONIST, APPL. **DRUG SCREENING**, SYSTEMIC LUPUS ERYTHEMATOSIS, RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, JUVENILE CHRONIC ARTHRITIS, SPONDYLOARTHROPATHY, SYSTEMIC SCLEROSIS, IDIOPATHIC INFLAMMATORY MYOPATHY, SJOGREN SYNDROME, SYSTEMIC VASCULITIS, SARCOIDOSIS, AUTOIMMUNE HEMOLYTIC ANEMIA, AUTOIMMUNE THROMBOCYTOPENIA, THYROIDITIS, DIABETES MELLITUS, IMMUNE-MEDIATED RENAL DISEASE, DEMYELINATING DISEASE, CENTRAL, PERIPHERAL NERVOUS SYSTEM, IDIOPATHIC DEMYELINATING POLYNEUROPATHY, GUILLAIN-BARRE SYNDROME, CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY, HEPATOBILIARY DISEASE, INFECTIOUS, AUTOIMMUNE CHRONIC ACTIVE HEPATITIS, PRIMARY BILIARY CIRRHOSIS, GRANULOMATOUS HEPATITIS, SCLEROSING CHOLANGITIS, INFLAMMATORY BOWEL DISEASE, GLUTEN-SENSITIVE ENTEROPATHY, WHIPPLE DISEASE, AUTOIMMUNE, IMMUNE MEDIATED SKIN DISEASE, BULLOUS SKIN DISEASE, ERYTHEMA MULTIFORME, CONTACT DERMATITIS, PSORIASIS, ALLERGIC DISEASE, ASTHMA, ALLERGIC RHINITIS, ATOPIC DERMATITIS, FOOD HYPERSENSITIVITY, URTICARIA, LUNG IMMUNOLOGIC DISEASE, EOSINOPHILIC PNEUMONIA, IDIOPATHIC PULMONARY FIBROSIS, HYPERSENSITIVITY PNEUMONITIS, TRANSPLANTATION ASSOCIATED DISEASE, GRAFT REJECTION, GRAFT-VERSUS-HOST DISEASE DIAGNOSIS, THERAPY, MAPPING, CHROMOSOME IDENTIFICATION, TISSUE TYPING, ANTISENSE SEQUENCE, TRANSGENIC ANIMAL, MOL.WT. MARKER, GENE THERAPY CELL CULTURE CHINESE HAMSTER OVARY ANIMAL MAMMAL BACTERIUM FUNGUS ANTIBODY ENGINEERING ANTIALLERGIC ANTIINFLAMMATORY ANTIASTHMATIC ANTIANEMIC IMMUNOSUPPRESSIVE NEUROPROTECTIVE ANTIDIABETIC ANTIRHEUMATIC HEPATOTROPIC ANTIPSORIATIC ANTITHYROID (23, 11)

L115 ANSWER 38 OF 42 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2003-28416 BIOTECHDS
TITLE: New human IL-17 homologous polypeptides useful for e.g. treating and diagnosing immune-related disorders in mammals e.g. systemic lupus erythematosis or rheumatoid arthritis, and for identifying antagonists and agonists; vector-mediated **interleukin**-17 homolog gene transfer and expression in host cell for recombinant protein production, **drug screening** and gene therapy

Searched by Barb O'Bryen, STIC 2-2518

AUTHOR: CHEN J; FILVAROFF E; FONG S; GODDARD A; GODOWSKI P J; GRIMALDI C; GURNEY A; LI H; HILLAN K; TUMAS D; VANLOOKEREN M; VANDLEN R; WATANABE C; WILLIAMS P M; WOOD W I; YANSURA D
PATENT ASSIGNEE: GENENTECH INC
PATENT INFO: US 2003186306 2 Oct 2003
APPLICATION INFO: US 2003-410374 8 Apr 2003
PRIORITY INFO: US 2003-410374 8 Apr 2003; WO 2000-23328 24 Aug 2000
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2003-803149 [75]
ABSTRACT: DERWENT ABSTRACT:
NOVELTY - A polypeptide having at least 80 % identity to one of eight amino acid sequences (I)-(VIII) respectively for a human IL-17 homologous polypeptide (PRO polypeptide) designated PRO1031, PRO1122, PRO10272, PRO21175, PRO5801, PRO20040, PRO9877 and PRO20026 respectively (or an extracellular domain of the polypeptide or polypeptide/extracellular domain lacking associated signal peptide) is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) a polynucleotide having at least 80 % identity to a polynucleotide encoding a polypeptide as above, especially to one of sequences (IX)-(XVI) encoding (I)-(VIII) respectively and included in cDNA deposits ATCC 209866, 203552, PTA-1185, PTA-2108, PTA-202, PTA-1535, PTA-1082 and PTA-2591 respectively; (2) vectors comprising a polynucleotide as in (1); (3) host cells comprising the vector; (4) chimeric molecule comprising polypeptide fused to a heterologous amino acid sequence (optionally an epitope tag sequence or FC region of an immunoglobulin); (5) antibodies (optionally monoclonal, humanized or single-chain) specifically binding polypeptide; and (6) compositions comprising carrier and polypeptide, agonist/antagonist of polypeptide or antibody as in (5).

WIDER DISCLOSURE - A further PRO polypeptide PRO20110 having defined 163 amino acid sequence encoded by defined 559 bp sequence (sequences given in the specification) is included but not claimed.

BIOTECHNOLOGY - Preparation: Polypeptide can be produced by **culturing** host cells of (3) under suitable conditions for polypeptide expression and recovering polypeptide from **culture.** Preferred Host Cells: Host cells are preferably CHO, E. coli, yeast or Baculovirus-infected insect cells.

ACTIVITY - Immunosuppressant; Antiarthritic; Antiinflammatory;Antorheumatic;Osteopathic.

USE - The polypeptides (and antibodies as in (5) and agonists/antagonists identified using polypeptides) are useful to treat immune-related disorders in mammals e.g. systemic lupus erythematosis, rheumatoid arthritis, osteoarthritis etc. . A PRO1031 or PRO10272 polypeptide (or agonist/antagonist) can be administered to treat a degenerative cartilaginous disorder , or a PRO1031 polypeptide or agonist/antibody/antagonist administered to stimulate/inhibit angiogenesis . PRO1031 or PRO10272 polypeptides (or agonists) are especially useful to stimulate/inhibit proliferation of T-lymphocytes in mammals or enhance/decrease infiltration of inflammatory cells (e.g. mononuclear cells, **eosinophils** etc.) into a mammalian tissue. The polypeptides, agonists, antagonists and

antibodies may be included with a pharmaceutical carrier in compositions (claimed), useful as above to treat immune-related diseases in mammals , especially by increasing/inhibiting T-lymphocyte proliferation or increasing/decreasing infiltration of inflammatory cells into mammalian tissue. The polypeptides may also be used to diagnose an immune related disease or to detect a tumor (e.g. a lung, colon or breast tumor) in mammals, by detecting increased PRO polypeptide expression in sample cells . They can be used to identify inhibitory compounds or compounds mimicking PRO polypeptide activity . They can also be used to detect PRO polypeptides in samples, modulate one or more biological activities of PRO polypeptide-expressing cells (e.g. to kill the cells) or to link a bioactive molecule to PRO polypeptide-expressing cells (e.g. a toxin to cause cell death). The antibodies are useful to detect PRO polypeptides in samples and to diagnose immune related diseases in mammals . The polynucleotides can also be used to diagnose immune related diseases in mammals and to identify compounds inhibiting PRO gene expression e.g. antisense polynucleotides (all claimed).

EXAMPLE - Extracellular domain sequences of 950 known secreted proteins from Swiss-Prot public database were used to search public (e.g. GenBank) and proprietary LIFESEQ (RTM) expressed sequence tag databases using BLAST or BLAST2 computer programs (Altshul et al., Methods in Enzymology, 266:460-480 (1996)). Comparisons giving BLAST score over 70 and not encoding known proteins were clustered and assembled into consensus sequences with known program 'phrap'. Initial consensus sequence was extended with repeated cycles of BLAST and phrap, giving DNA47332. One sequence comprising consensus assembly was obtained from the IMAGE consortium (Lennon et al., Genomics, 33:151 (1996)) and sequenced, giving sequence (IX) encoding PRO1031 sequence (I). (154 pages)

CLASSIFICATION: THERAPEUTICS, Protein Therapeutics; GENETIC TECHNIQUES and APPLICATIONS, Gene Expression Techniques and Analysis; GENETIC TECHNIQUES and APPLICATIONS, Genomic Technologies; BIOINFORMATICS and ANALYSIS, Software; BIOINFORMATICS and ANALYSIS, Databases; DISEASE, Cancer; DISEASE, Autoimmune Disease; DISEASE, Other Diseases; BIOMANUFACTURING and BIOCATALYSIS, Animal/Plant Cell Culture; DIAGNOSTICS, Molecular Diagnostics; DIAGNOSTICS, Antibody-Based Diagnostics; THERAPEUTICS, Gene Therapy

CONTROLLED TERMS: HUMAN RECOMBINANT **INTERLEUKIN**-17 PRO PROTEIN HOMOLOG PREP., VECTOR-MEDIATED GENE TRANSFER, EXPRESSION IN CHO CELL, ESCHERICHIA COLI, YEAST HOST CELL, BACULO VIRUS-INFECTED INSECT CELL, MONOCLONAL ANTIBODY, HUMANIZED ANTIBODY, SINGLE CHAIN ANTIBODY, ANTISENSE OLIGONUCLEOTIDE, AGONIST, ANTAGONIST, EXPRESSED SEQUENCE TAG DATABASE, BLAST COMPUTER BIOINFORMATIC SOFTWARE, APPL. **DRUG SCREENING**, IMMUNE-RELATED DISORDER, SYSTEMIC LUPUS ERYTHEMATOSIS, RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, DEGENERATIVE CARTILAGINOUS DISORDER, LUNG, COLON, MAMMA CANCER THERAPY, DIAGNOSIS, GENE THERAPY ANIMAL MAMMAL **CYTOKINE** PROTEIN LYMPHOKINE CHINESE HAMSTER OVARY CELL **CULTURE** BACTERIUM FUNGUS ARTHROPOD ANTIBODY ENGINEERING BIOINFORMATICS TUMOR DNA SEQUENCE PROTEIN SEQUENCE (22, 51)

L115 ANSWER 39 OF 42 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN

ACCESSION NUMBER: 2003-22452 BIOTECHDS
TITLE: New isolated IL-17 nucleic acids and polypeptides, useful for diagnosing and treating disorders with aberrant expression or activity of the IL-17 polypeptide, such as degenerative cartilaginous and immune-related disorders; recombinant protein production and antagonist and agonist for use in disease therapy and gene therapy
AUTHOR: CHEN J; FILVAROFF E; FONG S; FRENCH D; GODDARD A; GODOWSKI P J; GRIMALDI J C; GURNEY A L; HILLAN K J; HYMOWITZ S G; LI H; PAN J; STAROVASNIK M A; TUMAS D; VAN LOOKEREN M; VANDLEN R; WATANABE C K; WILLIAMS P M; WOOD W I; YANSURA D G
PATENT ASSIGNEE: GENENTECH INC
PATENT INFO: US 2002182673 5 Dec 2002
APPLICATION INFO: US 2001-157 30 Oct 2001
PRIORITY INFO: WO 2001-21735 9 Jul 2001; WO 1999-5028 8 Mar 1999
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2003-605678 [57]
ABSTRACT: DERWENT ABSTRACT:
NOVELTY - An isolated nucleic acid (I) comprising at least 80% identity to a nucleotide sequence encoding a polypeptide or an extracellular domain of a polypeptide with any of 9 fully defined sequences of 163-728 amino acids, given in the specification, is new.

DETAILED DESCRIPTION - An isolated nucleic acid (I) comprising at least 80% identity to a nucleotide sequence encoding a polypeptide or an extracellular domain of a polypeptide with any of 9 fully defined sequences of 163-728 amino acids, given in the specification, lacking or with its associated signal peptide, and has any of 9 fully defined sequences or full-length coding sequences of 556-2358 base pairs, given specification, or has DNA deposited under ATCC accession number 209866, 203552, PTA-1185, PTA-2108, PTA202, PTA-1535, PTA-1082 or PTA-2591, is new. INDEPENDENT CLAIMS are also included for the following: (1) a vector comprising (I); (2) a host cell comprising the vector of (1); (3) producing a PRO polypeptide comprising **culturing** the host cell of (2) under conditions suitable for expression of the polypeptide, and recovering the polypeptide from the cell **culture**; (4) an isolated polypeptide (II) encoded by (I), and having at least 80% sequence identity to any of 9 fully defined sequences of 163-728 amino acids, given in the specification; (5) a chimeric molecule comprising (II) fused to a heterologous amino acid sequence; (6) an antibody which specifically binds to (II); (7) a composition of matter comprising (II), an agonist or antagonist of (II), or an antibody of (6), in combination with a carrier; (8) an article of manufacture comprising a container, a label on the container, and the composition of (7), where the label indicates that the composition of matter can be used for treating an immune related disease; (9) treating an immune related disorder in a mammal, comprising administering (II), an agonist or antagonist of (II), or an antibody of (6); (10) determining the presence of a PRO1031, PRO1122, PRO10272, PRO21175, PRO20110, PRO5801, PRO20040 or PRO20026 polypeptide in a sample; (11) diagnosing an immune related disease in a mammal; (12) identifying a compound that inhibits or mimics the activity of or the expression of a gene encoding a PRO1031, PRO1122, PRO10272, PRO21175, PRO20110, PRO5801, PRO20040, PRO9877 or PRO20026 polypeptide;

(13) stimulating proliferation of T-lymphocytes or enhancing infiltration of inflammatory cells; (14) inhibiting proliferation of T-lymphocytes or decreasing infiltration of inflammatory cells into a tissue of a mammal; (15) inhibiting angiogenesis induced by a PRO1031 polypeptide or its agonist in a mammal, comprising administering an anti-PRO1031 antibody or an antagonist of the polypeptide to the mammal; (16) stimulating angiogenesis induced by a PRO1031 polypeptide or its agonist in a mammal, comprising administering the polypeptide, where angiogenesis is stimulated; (17) treating a degenerative cartilaginous disorder in a mammal; (18) a kit comprising a composition comprising a PRO1031 polypeptide with a fully defined sequence of 180 amino acids, a PRO1122 polypeptide with a fully defined sequence of 196 amino acids, a PRO20110 or PRO10272 polypeptide with a fully defined sequence of 163 amino acids, all given in the specification, or their agonist and antagonist, in admixture with a carrier, and a container containing the composition, and with a label affixed to the container, or a package insert included in the container referring to the use of the composition, in the treatment of a degenerative cartilaginous disorder; (19) detecting a polypeptide designated as A, B, or C, or detecting a polypeptide designated as D, E or F in a sample suspected of containing an A, B, or C, or an D, E or F polypeptide; (20) linking a bioactive molecule to a cell expressing a polypeptide designated as A, B, or C, or D, E or F; (21) modulating at least one biological activity of a cell expressing a polypeptide designated as A, B, or C, or D, E or F; and (22) detecting the presence of a tumor in a mammal, comprising comparing the level of expression of any PRO polypeptide in a test sample of cells taken from the mammal and a control sample of normal cells of the same cell type, where a higher level of expression of the PRO polypeptide in the test sample as compared to the control sample is indicative of the presence of tumor in the mammal.

BIOTECHNOLOGY - Preferred Vector: The vector is operably linked to control sequences recognized by a host cell transformed with the vector. Preferred Host Cell: The cell is preferably a CHO, an E. coli, a yeast or a Baculovirus infected insect cell. Preferred Chimeric Molecule: The heterologous amino acid sequence in the chimeric molecule is an epitope tag sequence or an Fc region of an immunoglobulin. Preferred Antibody: The antibody is a monoclonal, humanized or a single-chain antibody. Preferred Composition: The composition is capable of increasing or inhibiting proliferation of T-lymphocytes and/or increasing or decreasing the infiltration of inflammatory cells into a tissue of a mammal. Preferred Method: Determining the presence of a PRO1031, PRO1122, PRO10272, PRO21175, PRO20110, PRO5801, PRO20040 or PRO20026 polypeptide in a sample, comprises exposing the sample to an anti-PRO1031, anti-PRO1122, anti-PRO10272, anti-PRO21175, anti-PRO20110, anti-PRO5801, anti-PRO20040 or anti-PRO20026 antibody, and determining binding of the antibody to a component of the sample. Diagnosing an immune related disease in a mammal, comprises detecting the level of expression of a gene encoding PRO1031, PRO1122, PRO10272, PRO21175, PRO20110, PRO5801, PRO20040, PRO9877 or PRO20026 polypeptide in a test sample of tissue cells obtained from the mammal, and in a

control sample of known normal tissue cells of the same cell type, where a higher or lower level of expression of the gene in the test sample as compared to the control sample is indicative of the presence of an immune related disease in the mammal from which the test tissue cells were obtained, or contacting an anti-PRO1031, anti-PRO1122, anti-PRO10272, anti-PRO21175, anti-PRO20110, anti-PRO5801, anti-PRO20040, anti-PRO9877 or anti-PRO20026 antibody with a test sample of tissue cells obtained from the mammal and determining the formation of a complex between the antibody and the polypeptide in the sample, where formation of the complex is indicative of the presence of an immune related disease in the mammal from which the test tissue cells were obtained. Identifying a compound that inhibits or mimics the activity of or the expression of a gene encoding a PRO1031, PRO1122, PRO10272, PRO21175, PRO20110, PRO5801, PRO20040, PRO9877 or PRO20026 polypeptide, comprises contacting cells which normally respond to or express the polypeptide with the polypeptide and a candidate compound, and determining the lack of responsiveness by the cell to the candidate compound or expression of the gene. The candidate compound is an antisense nucleic acid. Stimulating proliferation of T-lymphocytes or enhancing infiltration of inflammatory cells, comprises contacting T-lymphocytes with or administering (II) or an agonist of (II), where the proliferation of T-lymphocytes is stimulated or infiltration is enhanced. Inhibiting proliferation of T-lymphocytes or decreasing infiltration of inflammatory cells into a tissue of a mammal, comprises contacting T-lymphocytes with or administering an antagonist of a PRO1031 or PRO10272 polypeptide, where the proliferation of T-lymphocytes or infiltration is decreased. The inflammatory cells in the method of (13) or (14) are mononuclear cells, **eosinophils** or polymorphonuclear neutrophils. Inhibiting angiogenesis induced by a PRO1031 polypeptide or its agonist in a mammal, comprises administering an anti-PRO1031 antibody or an antagonist of the polypeptide to the mammal. Stimulating angiogenesis induced by a PRO1031 polypeptide or its agonist in a mammal, comprises administering the polypeptide, where angiogenesis is stimulated. Treating a degenerative cartilaginous disorder in a mammal comprises administering a PRO1031, PRO1122, PRO10272 or PRO20110 polypeptide, agonist or antagonist, to the mammal suffering from the disorder. Detecting a polypeptide designated as A, B, or C, or detecting a polypeptide designated as D, E or F in a sample suspected of containing an A, B, or C, or an D, E or F polypeptide, respectively, comprises contacting the sample with a polypeptide designated as D, E, or F, or A, B or C, respectively, and determining the formation of a A/D, B/D, C/E or C/F polypeptide conjugate in the sample, where the formation of the conjugate is indicative of the presence of an A, B, or C polypeptide in the sample, and where A is a PRO1031 polypeptide (IL-17B), B is a PRO10272 polypeptide (IL-17E), C is a PRO20110 polypeptide (IL-17F), D is a PRO5801 polypeptide (IL-17RH1), E is a PRO1 polypeptide (IL-17R), and F is a PRO20040 polypeptide (IL-17RH2). The sample comprises cells suspected of expressing the A, B or C, or D, E or F polypeptide. The D, E or F, or A, B or C is preferably labeled with a detectable label, and is attached to a solid support. Linking a

bioactive molecule to a cell expressing a polypeptide designated as A, B, or C, or D, E or F, comprises contacting the cell with a polypeptide designated as D, E, or F, or A, B or C, respectively, that is bound to the bioactive molecule, and allowing the A, B, or C and the D, E, or F polypeptides to bind to one another, therefore linking the bioactive molecules to the cell, where A is a PRO1031 polypeptide, B is a PRO10272 polypeptide, C is a PRO20110 polypeptide, D is a PRO5801 polypeptide, E is a PRO1 polypeptide, and F is a PRO20040 polypeptide. The bioactive material is a toxin, a radiolabel or an antibody, and causes the death of the cell. Modulating at least one biological activity of a cell expressing a polypeptide designated as A, B, or C, or D, E or F, comprises contacting the cell with a polypeptide designated as D, E, or F, or A, B or C, respectively, or an anti-A, anti-B, or anti-C, or an anti-D, anti-E or anti-F polypeptide antibody, respectively, where the polypeptide or antibody binds to the A, B, or C, or D, E or F polypeptide, therefore modulating at least one biological activity of the cell, where A is a PRO1031 polypeptide, B is a PRO10272 polypeptide, C is a PRO20110 polypeptide, D is a PRO5801 polypeptide, E is a PRO1 polypeptide, and F is a PRO20040 polypeptide. The cell is killed. Detecting the presence of a tumor in a mammal, comprises comparing the level of expression of any PRO polypeptide in a test sample of cells taken from the mammal and a control sample of normal cells of the same cell type, where a higher level of expression of the PRO polypeptide in the test sample as compared to the control sample is indicative of the presence of tumor in the mammal. The tumor is a lung, colon or breast tumor.

ACTIVITY - Immunosuppressive; Osteopathic; Antiarthritic; Antirheumatic; Antiinflammatory; Antithyroid; Antidiabetic; Cerebroprotective; Neuroprotective; Nootropic; Hepatotropic; Gastrointestinal; Dermatological; Antiallergic; Antipsoriatic; Antiasthmatic.

MECHANISM OF ACTION - **Interleukin**-Agonist-17; **Interleukin**-Antagonist-17. To examine the role of expression of IL-17 family members in a mice deficient in the **cytokine** receptor CRF2-4/IL-10Rb with spontaneous and progressive colitis. The results showed that the expression of IL-17E markedly decreases in more advanced severe inflammatory bowel disease compared to expression levels in normal mice. Therefore, IL-17E may serve as a marker for this inflammatory condition.

USE - The methods and compositions of the present invention are useful for diagnosing and treating disorders associated with the aberrant expression or activity of a PRO polypeptide. The disorders include a degenerative cartilaginous disorder and immune related diseases, such as systemic lupus erythematosis, rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, spondyloarthropathy, systemic sclerosis, an idiopathic inflammatory myopathy, Sjogren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia, autoimmune thrombocytopenia, thyroiditis, diabetes mellitus, immune-mediated renal disease, a demyelinating disease of the central or peripheral nervous system, idiopathic demyelinating polyneuropathy, Guillain-Barre syndrome, a chronic inflammatory demyelinating polyneuropathy, a hepatobiliary disease, infectious or autoimmune chronic

active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, sclerosing cholangitis, inflammatory bowel disease, gluten-sensitive enteropathy, Whipple's disease, an autoimmune or immune-mediated skin disease, a bullous skin disease, erythema multiforme, contact dermatitis, psoriasis, an allergic disease, asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity, urticaria, an immunologic disease of the lung, eosinophilic pneumonia, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, a transplantation-associated disease, graft rejection or graft-versus-host-disease (claimed).

ADMINISTRATION - Dosage of the pharmaceutical composition ranges from 1-15 mg/kg body weight. Routes of administration include oral, pulmonary, intramuscular, intraperitoneal, intravenous, subcutaneous, inhalation, transdermal, nasal and vaginal.

EXAMPLE - An expressed sequence tag (EST) DNA database was searched and an EST was identified. The EST was Incyte 1347523 also called DNA49665. Based on DNA49665, oligonucleotides were synthesized. Forward and reverse PCR primers were then used for hybridization, and the library screened to isolate clones encoding the PRO1122 gene. DNA sequencing of the clones isolated gave the full length DNA sequence for PRO1122 with a fully defined sequence of 1046 base pairs, given in the specification. (161 pages)

CLASSIFICATION: THERAPEUTICS, Protein Therapeutics; GENETIC TECHNIQUES and APPLICATIONS, Gene Expression Techniques and Analysis; DISEASE, Blood and Hematopoietic Cells; DISEASE, Central Nervous System; DISEASE, Endocrine/Metabolic System; DISEASE, Autoimmune Disease; DISEASE, Other Diseases; BIOMANUFACTURING and BIOCATALYSIS, Animal/Plant Cell Culture; PHARMACEUTICALS, Antibodies; THERAPEUTICS, Gene Therapy; DISEASE, Respiratory System; DISEASE, Liver

CONTROLLED TERMS: RECOMBINANT **INTERLEUKIN**-17 PROTEIN, PRO PROTEIN, PRO1031, PRO1122, PRO10272, PRO21175, PRO20110, PRO5801, PRO20040, PRO20026, PREP., VECTOR-MEDIATED GENE TRANSFER EXPRESSION IN CHO, ESCHERICHIA COLI, YEAST, BACULO VIRUS INSECT HOST CELL, FUSION PROTEIN, MONOCLONAL ANTIBODY, HUMANIZED ANTIBODY, SINGLE CHAIN ANTIBODY, ANTAGONIST, AGONIST, APPL. **DRUG SCREENING**, DEGENERATIVE CARTILAGINOUS DISORDER, IMMUNE RELATED DISEASE, SYSTEMIC LUPUS ERYTHEMATOSIS, RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, JUVENILE CHRONIC ARTHRITIS, SPONDYLOARTHROPATHY, SYSTEMIC SCLEROSIS, IDIOPATHIC INFLAMMATORY MYOPATHY, SJOGREN SYNDROME, SYSTEMIC VASCULITIS, SARCOIDOSIS, AUTOIMMUNE HEMOLYTIC ANEMIA, AUTOIMMUNE THROMBOCYTOPENIA, THYROIDITIS, DIABETES MELLITUS, IMMUNE-MEDIATED RENAL DISEASE, DEMYELINATING DISEASE,CENTRAL OR PERIPHERAL NERVOUS SYSTEM, IDIOPATHIC DEMYELINATING POLYNEUROPATHY, GUILLAIN-BARRE SYNDROME, CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY, HEPATOBILIARY DISEASE, INFECTIOUS, AUTOIMMUNE CHRONIC ACTIVE HEPATITIS, PRIMARY BILIARY CIRRHOSIS, GRANULOMATOUS HEPATITIS, SCLEROSING CHOLANGITIS, INFLAMMATORY BOWEL DISEASE, GLUTEN-SENSITIVE ENTEROPATHY, WHIPPLE DISEASE, IMMUNE-MEDIATED SKIN DISEASE, BULLOUS SKIN DISEASE, ERYTHEMA MULTIFORME, CONTACT DERMATITIS, PSORIASIS, ALLERGIC DISEASE, ASTHMA, ALLERGIC RHINITIS, ATOPIC DERMATITIS, FOOD HYPERSENSITIVITY, URTICARIA, IMMUNOLOGIC DISEASE, LUNG DISEASE, EOSINOPHILIC PNEUMONIA, IDIOPATHIC PULMONARY FIBROSIS, HYPERSENSITIVITY

PNEUMONITIS, TRANSPLANTATION-ASSOCIATED DISEASE, GRAFT REJECTION, GRAFT-VERSUS-HOST-DISEASE DIAGNOSIS, THERAPY, GENE THERAPY CYTOKINE PROTEIN CELL CULTURE CHINESE HAMSTER OVARY ANIMAL MAMMAL BACTERIUM FUNGUS ARTHROPOD ANTIBODY ENGINEERING IMMUNOSUPPRESSIVE OSTEOPATHIC ANTIRHEUMATIC ANTIINFLAMMATORY ANTITHYROID ANTIDIABETIC CEREBROPROTECTIVE NEUROPROTECTIVE NOOTROPIC HEPATOTROPIC ANTIALLERGIC ANTIPSORIATIC ANTIASTHMATIC DNA SEQUENCE PROTEIN SEQUENCE (22, 38)

L115 ANSWER 40 OF 42 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2003-22451 BIOTECHDS
TITLE: Novel polypeptides having sequence similarity to **interleukin**-17 and **interleukin**-17 receptor protein useful for treating, diagnosing immune related disorders and treating degenerative cartilaginous disorder in a mammal;
involving vector-mediated gene transfer and expression in Chinese hamster ovary, Escherichia coli or yeast cell for use in gene therapy
AUTHOR: CHEN J; FILVAROFF E; FONG S; GODDARD A; GODOWSKI P J; GRIMALDI J C; GURNEY A; LI H; HILLAN K; HYMOWITZ S G; TUMAS D; STARVOVASNIK M A; LOOKEREN M V; VANDLEN R; WATANABE C; WILLIAMS P M; WOOD W I; YANSURA D G
PATENT ASSIGNEE: GENENTECH INC
PATENT INFO: US 2002177188 28 Nov 2002
APPLICATION INFO: US 2001-874503 5 Jun 2001
PRIORITY INFO: WO 2001-6520 28 Feb 2001; WO 1999-5028 8 Mar 1999
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2003-605676 [57]
ABSTRACT: DERWENT ABSTRACT:
NOVELTY - An isolated polypeptide (I) having at least 80% amino acid sequence identity to **interleukin**(IL)-17 and IL-17 receptor protein sequences fully given in the specification, or to an amino acid sequence encoded by full length coding sequence of DNA deposited under ATCC Accession Number 209866, 203552, PTA-1185, PTA-2108, PTA-202, PTA-1535, PTA-1082 or PTA-2591, is new.

DETAILED DESCRIPTION - (I) has at least 80% amino acid sequence identity to amino acid sequence of 9 **interleukin**(IL)-17 and IL-17 receptor proteins (PRO polypeptides) which includes PRO1031, PRO1122, PRO10272, PRO21175, PRO20110, PRO5801, PRO20040, PRO9877 and PRO20026 whose sequences are fully given in the specification; amino acid sequence of PRO polypeptides with or without its associated signal peptide; amino acid sequence of an extracellular domain of PRO polypeptide with or without its associated signal peptide; or an amino acid sequence encoded by full length coding sequence of DNA deposited under ATCC Accession Number 209866, 203552, PTA-1185, PTA-2108, PTA-202, PTA-1535, PTA-1082 or PTA-2591. INDEPENDENT CLAIMS are also included for: (1) an isolated nucleic acid (II) having at least 80% nucleic acid sequence identity to a nucleotide sequence that encodes the PRO polypeptides as above, or to the full-length coding sequence of the DNA deposited under ATCC Accession Number as above; (2) a vector (III) comprising (II); (3) a host cell comprising (III); (4) producing PRO polypeptides; (5) a chimeric molecule (IV) comprising (I) fused to a heterologous amino acid sequence; (6) an isolated antibody (V) that binds specifically to (I); (7) a

composition of matter (VI) comprising (I), agonist or antagonist of (I), or (V), with a carrier; (8) an article of manufacture comprising a container, a label on the container and (VI); (9) identifying a compound that mimics the activity of PRO polypeptide by contacting cells which normally respond to the polypeptide with a candidate compound, and determining the responsiveness by the cell to the candidate compound; and (10) a kit comprising (VI), a container containing PRO1031, PRO1122, PRO20110 or PRO10272 polypeptide, its agonist or antagonist, and a label affixed to the container, or a package insert included in the container, referring to the use of the composition, in the treatment of degenerative cartilaginous disorder.

WIDER DISCLOSURE - Disclosed are: (A) recombinant viral particle comprising a viral vector consisting of a nucleic acid encoding PRO polypeptide, its agonist or antagonist, and a signal sequence for cellular secretion of the polypeptide; (B) ex vivo producer cell comprising a nucleic acid construct that expresses retroviral structural proteins and retroviral vector as above; (C) oligonucleotide probes useful for isolating genomic and cDNA nucleotide sequences derived from (II); (D) heteroconjugate antibodies comprising (V); and (E) immunoconjugates comprising (V) conjugated to a cytotoxic agent.

BIOTECHNOLOGY - Preparation: PRO polypeptides are prepared by **culturing** Chinese Hamster ovary (CHO) cells or Escherichia coli, yeast cells comprising (III) under conditions suitable for expression of the polypeptide and recovering the PRO polypeptide from the cell **culture** (claimed). Preferred Vector: (III) operably linked to control sequences recognized by a host cell transformed with the vector. Preferred Molecule: In (IV), the heterologous amino acid sequence is an epitope tag sequence or an Fc region of an immunoglobulin. Preferred Antibody: (V) is a monoclonal, humanized or single-chain antibody.

ACTIVITY - Dermatological; Immunosuppressive; Antiinflammatory; Antirheumatic; Antiarthritic; Osteopathic; Antianemic; Antidiabetic; Antithyroid; Hemostatic; Hepatotropic; Antipsoriatic; Antiallergic; Antiasthmatic; Vasotropic.

MECHANISM OF ACTION - Gene therapy; Stimulator of immune response and inducer of inflammation. Skin vascular permeability assay showed that certain PRO polypeptides stimulated an immune response and induced inflammation by inducing mononuclear cell, **eosinophil** and PMN infiltration at the site of injection of the animal. This skin vascular permeability assay was conducted. Hairless guinea pigs weighing 350 g or more were anesthetized with ketamine (75-80 mg/kg) and 5 mg/kg xylazine intramuscularly (IM). A sample of purified PRO polypeptide or a conditioned media test sample was injected intradermally onto the backs of the test animals with 100 mul per injection site. One ml of Evans blue dye was injected intracardially. Blemishes at the injection sites were then measured (mm diameter) at 1 hour, 6 hours, and 24 hours post injection. Animals were sacrificed at 6 hours after injection. The skins were then prepared for histopathologic evaluation. Each site was evaluated for inflammatory cell infiltration into the skin. At least a minimal perivascular infiltrate at the injection site was scored as positive, no infiltrate at the site of

injection was scored as negative. PRO1031 gave positive results at time interval 24 hours in this assay.

USE - (VI) is useful for treating an immune related disorder such as systemic lupus erythematosus, rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, spondyloarthropathy, systemic sclerosis, idiopathic inflammatory myopathy, Sjogren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia, autoimmune thrombocytopenia, thyroiditis, diabetes mellitus, immune-mediated renal disease, demyelinating disease of the central or peripheral nervous system, idiopathic demyelinating polyneuropathy, Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, hepatobiliary disease, infectious or autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatus hepatitis, sclerosing cholangitis, inflammatory bowel disease, gluten-sensitive enteropathy, Whipple's disease, autoimmune or immune-mediated skin disease, bullous skin disease, erythema multiforme, contact dermatitis, psoriasis, allergic disease, asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity, urticaria, immunologic disease of the lung, eosinophilic pneumonia, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, transplantation associated disease or graft rejection or graft-versus-host-disease, in a mammal. (V) is useful for determining the presence of PRO polypeptide in a sample suspected of containing the polypeptide. (II) and (V) are useful for diagnosing an immune related disease in a mammal. (I) is useful for identifying a compound that inhibits the activity of PRO polypeptide or expression of gene encoding PRO polypeptide, by contacting cells which normally express the polypeptide with a candidate compound, and determining the lack of responsiveness by the cell or expression of the gene. PRO1031 or PRO10272 polypeptide or its agonist is useful for stimulating the proliferation of T-lymphocytes, and antagonist of PRO1031 or PRO10272 polypeptide is useful for inhibiting the proliferation of T-lymphocytes. PRO1031 polypeptide or its agonist is useful for enhancing the infiltration of inflammatory cells such as mononuclear cells, **eosinophils** or polymorphonuclear neutrophils (PMNs) into a tissue of a mammal, and antagonist of PRO1031 polypeptide is useful for decreasing the infiltration of inflammatory cells into a tissue of a mammal and for inhibiting angiogenesis. Anti-PRO1031 antibody is useful for inhibiting angiogenesis induced by a PRO1031 polypeptide or its agonist in a mammal. PRO1031 polypeptide is useful for stimulating angiogenesis induced by a PRO1031 polypeptide or its agonist in a mammal. PRO1031, PRO1122, PRO10272, PRO20110 polypeptide, its agonist or antagonist is useful for treating a degenerative cartilaginous disorder in a mammal. PRO5801, PRO1 or PRO20040 polypeptide is useful for detecting PRO1031, PRO10272 or PRO20110 polypeptide in a sample, or vice versa. PRO5801, PRO1 or PRO20040 polypeptide is useful for linking a bioactive molecule (e.g. toxin, radiolabel, antibody or a molecule which causes death of a cell), to a cell expressing a polypeptide such as PRO1031, PRO10272 or PRO20110 polypeptide, or vice versa. PRO5801, PRO1 or PRO20040 polypeptide or anti-PRO1031, anti-PRO10272 or anti-PRO20110 antibody is useful for modulating biological activity of a cell expressing PRO1031, PRO10272 or PRO20110 polypeptide, or

vice versa. Preferably, the cell is killed. PRO10272 (also designated IL-17E) and PRO5801 (also designated IL-17RH1) polypeptide is useful for detecting the presence of lung, colon or breast tumor in a mammal (all claimed). (II) is useful in molecular biology including uses as hybridization probes for cDNA library to isolate the full-length PRO cDNA or to isolate other cDNAs, in chromosome and gene mapping, and in the generation of antisense RNA and DNA, and for preparing PRO polypeptides. (II) is also useful for generating transgenic animals or knockout animals which are useful in the development and screening of therapeutically useful reagents. (II) is useful as probes for generating a pool of sequences for identifying related PRO coding sequences, and to construct hybridization probes for mapping the gene which encodes the PRO and for the genetic analysis of individuals with genetic disorders. (II) is useful for recombinantly expressing (I) and for chromosome identification. (I) is useful as molecular marker for protein electrophoresis purposes, and as therapeutic agents. (I) is also useful for **screening compounds** to identify those that mimic the PRO polypeptide (agonists) or prevent the effect of the PRO polypeptide (antagonists). (I) and (II) are useful for tissue typing. PRO antibodies are useful for immunohistochemical staining and/or assay of sample fluids. Anti-PRO antibodies are useful in diagnostic assays for PRO e.g. detecting its expression in specific cells, tissues or serum, and for affinity purification of PRO from recombinant cell **culture** or natural sources.

ADMINISTRATION - Administered by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial, intralesional or topical route. PRO polypeptide is administered at a dose of 10 ng-100 mg/kg, preferably 1 mug/kg-10 mg/kg/day.

EXAMPLE - The extracellular domain (ECD) sequences of 950 known secreted proteins from the Swiss-Prot public protein database were used to search expressed sequence tag (EST) databases, and a proprietary EST DNA database. The search was performed using the computer program BLAST or BLAST2. Those comparisons resulting in a BLAST score of 70 or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program phrap. An initial virtual sequence fragment was assembled relative to other EST sequences using phrap. The initial consensus DNA sequence was extended using repeated cycles of BLAST and phrap to extend the consensus sequence as far as possible using the sources of EST sequences. The results of this consensus assembly was referred to as DNA47332. One sequence comprising the consensus assembly, W74558 (clone 344649) was further examined. The sequence was obtained from the IMAGE consortium and analyzed. DNA sequencing gave the full-length DNA sequence for PRO1031, designated as DNA59294-1381. The entire nucleotide and protein sequence of DNA59294-1381 are fully given in the specification. Clone DNA59294-1381 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 42-44 and ending at the stop codon at nucleotide positions 582-584. The predicted polypeptide precursor was 180 amino acids long. Analysis of the amino acid sequence of the full-length PRO1031 polypeptide suggested that it was a novel **interleukin**-17 homolog, designated as IL-17B.

(140 pages)
CLASSIFICATION: THERAPEUTICS, Protein Therapeutics; GENETIC TECHNIQUES and APPLICATIONS, Gene Expression Techniques and Analysis; GENETIC TECHNIQUES and APPLICATIONS, Transgenic Animals and Animal Models; DISEASE, Central Nervous System; DISEASE, HIV and Other Virus Infections; DISEASE, Endocrine/Metabolic System; DISEASE, Respiratory System; DISEASE, Kidney; DISEASE, Autoimmune Disease; DISEASE, Infectious Disease (non-viral); DISEASE, Other Diseases; BIOMANUFACTURING and BIOCATALYSIS, Animal/Plant Cell Culture; PHARMACEUTICALS, Antibodies; DIAGNOSTICS, Molecular Diagnostics; THERAPEUTICS, Gene Therapy
CONTROLLED TERMS: RECOMBINANT PRO PROTEIN PREP., ISOL., VECTOR-MEDIATED GENE TRANSFER, EXPRESSION IN CHO, ESCHERICHIA COLI, YEAST CELL, AGONIST, ANTAGONIST, MONOCLONAL ANTIBODY, HUMANIZED ANTIBODY, SINGLE CHAIN ANTIBODY, TRANSGENIC ANIMAL MODEL CONSTRUCTION, ANTISENSE, APPL. SYSTEMIC LUPUS ERYTHEMATOSUS, RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, INFLAMMATION, AUTOIMMUNE DISORDER, ANEMIA, DIABETES MELLITUS, IMMUNE-MEDIATED KIDNEY DISEASE, CENTRAL NERVOUS SYSTEM DISORDER, INFECTION, CIRRHOSIS, SKIN DISEASE, ASTHMA, ALLERGY DIAGNOSIS, THERAPY, GENE THERAPY CHINESE HAMSTER OVARY ANIMAL MAMMAL BACTERIUM FUNGUS ANTIBODY ENGINEERING 6P21.3 DNA SEQUENCE PROTEIN SEQUENCE (22, 38)

L115 ANSWER 41 OF 42 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2003-04570 BIOTECHDS
TITLE: New human chemotactic **cytokine** III polypeptide useful for treating leukemia, tumors, chronic infections, autoimmune diseases, fibrotic disorders, wound healing, psoriasis, asthma and allergies;
vector-mediated recombinant protein gene transfer and expression in host cell for use in gene therapy, recombinant vaccine and nucleic acid vaccine preparation
AUTHOR: NI J; GENTZ R; YU G; SU J; DILLON P J
PATENT ASSIGNEE: HUMAN GENOME SCI INC
PATENT INFO: US 2002119528 29 Aug 2002
APPLICATION INFO: US 2001-986191 7 Nov 2001
PRIORITY INFO: US 2001-986191 7 Nov 2001; US 1996-13609 5 Mar 1996
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-731354 [79]
ABSTRACT: DERWENT ABSTRACT:
NOVELTY - A human chemotactic **cytokine** III (CCIII) polypeptide (I), comprising a sequence having 70 % identity to a polypeptide comprising: (i) a sequence (S1) comprising 81 amino acids fully defined in the specification; (ii) amino acids 1 - 53 of S1; or (iii) 15 amino acid residues of (i) or (ii), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) an isolated polynucleotide (II) comprising a polynucleotide having 70 % identity to a polynucleotide: (i) encoding a polypeptide comprising S1 or amino acids 1 - 53 of S1;(ii) encoding the same mature polypeptide expressed by the human cDNA contained in American Type **Culture** Collection (ATCC) Deposit Number 97406; (iii) a sequence complementary to (i) or (ii); or (iv) comprising 15 bases of (i) - (iii); (2) a vector (III) comprising (II); (3) a host cell (IV) comprising (III); (4) producing (I); (5) producing a cell expressing (I), by transforming or transfecting the cell with (III); (6) an

agonist (A1) of (I); (7) an antibody (Ab) specific to (I); (8) an antagonist (A2) which inhibits the activity of (I); (9) diagnosing a disease or a susceptibility to a disease related to expression of (I), comprising determining a mutation in the nucleic acid sequence encoding the polypeptide; and (10) identifying compounds which bind to and activate or inhibit a receptor for (I) with a **compound** to be **screened** under conditions to permit binding to the receptor, comprising: (a) contacting a cell expressing a receptor for (I) on its surface, where the receptor is associated with the second component capable of providing a detectable signal in response to the binding of the compound to the receptor; and (b) determining whether the compound binds to and activates or inhibits the receptor by detecting the presence or absence of a signal generated from the interaction of a compound with the receptor.

BIOTECHNOLOGY - Preparation: (I) is produced by expressing (I) from (IV), where (I) is encoded by a human cDNA (claimed). Preferred Sequence: (II) is a DNA or RNA, and comprises nucleotides 58 - 371 or 142 - 370 of a sequence S2 comprising 371 nucleotides, given in the specification. (II) encodes a polypeptide comprising amino acids 1 - 53 of S1.

ACTIVITY - Antitumor; Cytostatic; Antipsoriatic; Antiasthmatic; Antiallergic; Vulnerary; Antiarthritic; Antiarteriosclerotic; Immunosuppressive; Antiparasitic; Nephrotropic; Antiinflammatory; Vasotropic; Virucide.

MECHANISM OF ACTION - CCIII antagonist (claimed); Angiogenesis inhibitor; Hematopoiesis regulator; Gene therapy; Vaccine. No biological data is given.

USE - (I) is useful for treating a patient having a need for CCIII, by administering a therapeutically effective amount of (I), which involves providing the DNA encoding (I) to the patient and expressing (I) in vivo. An antagonist (A2) to (I) is useful for treating a patient having the need to inhibit CCIII polypeptide. (I) is also useful in a diagnostic process which comprises analyzing for the presence of (I) in a sample derived from a host (claimed). (I) is useful for treating tumors, chronic infections, leukemia, T-cell mediated autoimmune diseases, parasitic infections, psoriasis, asthma and allergy, for regulating hematopoiesis, to stimulate growth factor activity, to inhibit angiogenesis, and to promote wound healing. A2 is useful for treating and/or preventing glomerulonephritis, inflammation, cerebral ischemia, human T-cell lymphotropic virus (HTLV)-1 related diseases, arthritis, infectious diseases, autoimmune diseases, hypereosinophilic syndrome, endotoxic shock, atherosclerosis, allergies, bone marrow failure and asthma. (I) and nucleic acid (II) encoding (I) are useful as research reagents and materials for discovery of treatments and diagnostics to human disease. (I) is useful to inhibit bone marrow stem cell colony formation as an adjunct protective treatment during cancer chemotherapy and for leukemia. (I) is also employed to inhibit epidermal keratinocyte proliferation for treatment of psoriasis. (I) is also useful for enhancing host defenses against resistant chronic and acute infections e.g. mycobacterial infections, for inhibiting T cell proliferation, for increasing the presence of **eosinophils** in the conditions including schistosomiasis, trichinosis and ascariasis, and for treating fibrotic disorders including liver cirrhosis, osteoarthritis

and pulmonary fibrosis.

ADMINISTRATION - 10 micrograms - 8 mg/kg, preferably 10 micrograms - 1 mg, of (I) or an antagonist (A2) of (I) is administered through topical, oral, anal, vaginal, intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal or intradermal routes.

EXAMPLE - A DNA sequence encoding human chemotactic chemokine (CCIII) in a deposited polynucleotide was amplified using polymerase chain reaction (PCR) oligonucleotide primers specific to the amino acid carboxyl terminal sequence of the human CCIII protein and to vector sequences 3' to the gene. Additional nucleotides containing restriction sites to facilitate cloning were added to the 5' and 3' sequences, respectively. The 5' oligonucleotide primer had the sequence (P1) containing a NcoI restriction site, which encoded a start aug, followed by 16 nucleotides of the human CCIII coding sequence. The 3' primer had the sequence (P2) containing the underlined BamHI restriction site followed by 15 nucleotides complementary to CCIII non-coding sequence including the stop codon. The restriction sites were convenient to restriction enzyme sites in the bacterial expression vectors pQE-7 which were used for bacterial expression. pQE-7 encoded ampicillin antibiotic resistance (Ampr) and contained a bacterial origin of replication (ori), isopropyl-B-D-thiogalactopyranoside (IPTG) inducible promoter, a ribosome binding site (RBS), a 6-His tag and restriction enzyme sites. The amplified human CCIII DNA and the vector pQE-7 both were digested with NcoI and HindIII and the digested DNAs then were ligated together. Insertion of the CCII DNA into the NcoI/Hindm restricted vector placed the CCIII coding region downstream of and operably linked to the vector's IPTG-inducible promoter and in-frame with an initiating aug appropriately positioned for translation of CCIII. The ligation mixture was transformed into competent Escherichia coli cells using standard procedures. Transformants were identified by their ability to grow on Luria-Bertani medium (LB) plates in the presence of ampicillin. Plasmid DNA was isolated from resistant colonies and the identity of the cloned DNA was confirmed by restriction analysis. Clones containing the desired constructs were grown overnight (O/N) in liquid **culture** in LB media supplemented with both ampicillin (100 micrograms/ml) and kanamycin (25 micrograms/ml). The O/N **culture** was used to inoculate a large **culture** , at a dilution of approximately 1:100 to 1:250. The cells were grown to an optical density at 600 nm of between 0.4 and 0.6. IPTG was then added to a final concentration of 1 mM to induce transcription from lac repressor sensitive promoters, by inactivating the lacI repressor. Cells subsequently were incubated further for 3 to 4 hours. Cells then were harvested by centrifugation and disrupted and protein was solubilized from the inclusion bodies into 8 M urea. The protein was then purified by chromatography. 5'-cgcccatggtggccgccgcgcagg-3' (P1) 5'-cgcaagcttgcagagctcaattta-3' (P2)(28 pages)

CLASSIFICATION: THERAPEUTICS, Protein Therapeutics; GENETIC TECHNIQUES and APPLICATIONS, Gene Expression Techniques and Analysis; DISEASE, Cancer; DISEASE, Respiratory System; DISEASE, Autoimmune Disease; DISEASE, Infectious Disease (non-viral); PHARMACEUTICALS, Vaccines; THERAPEUTICS, Gene Therapy; DISEASE, Blood and Hematopoietic Cells; DISEASE, Liver;

DIAGNOSTICS, Molecular Diagnostics; DISEASE, Cardiovascular
CONTROLLED TERMS: HUMAN RECOMBINANT CHEMOTACTIC **CYTOKINE**-III PREP., ISOL., VECTOR-MEDIATED GENE TRANSFER, EXPRESSION IN HOST CELL, ANTIBODY, AGONIST, ANTAGONIST, APPL. LEUKEMIA, CANCER, CHRONIC INFECTION, AUTOIMMUNE DISEASE, FIBROTIC DISORDER, VULNERARY, PSORIASIS, ASTHMA, ALLERGY, LIVER DISEASE, CARDIOVASCULAR DISEASE DIAGNOSIS, THERAPY, GENE THERAPY, RECOMBINANT VACCINE, NUCLEIC ACID VACCINE PREP. ANIMAL MAMMAL PROTEIN TUMOR DNA SEQUENCE PROTEIN SEQUENCE (22, 8)

L115 ANSWER 42 OF 42 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2002-05639 BIOTECHDS
TITLE: Novel purified human **eosinophil** serine protease 1-like enzyme, useful for identifying modulators of enzyme activity for treating Paget's disease, osteoporosis, airway allergy, asthma;
involving vector-mediated gene transfer for expression in host cell, for use in **drug screening** and disease diagnosis and therapy
AUTHOR: XIAO Y
PATENT ASSIGNEE: BAYER AG
PATENT INFO: WO 2001098503 27 Dec 2001
APPLICATION INFO: WO 2000-EP6936 21 Jun 2000
PRIORITY INFO: US 2001-279766 30 Mar 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-122283 [16]
ABSTRACT: DERWENT ABSTRACT:
NOVELTY - A purified human **eosinophil** serine protease (esp) 1-like enzyme (I) having a a 339, 279, 334, 305 or 259 residue amino acid sequence, fully defined in the specification, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) an isolated polynucleotide (II): (a) encoding (I) which comprises an amino acid sequence of PS or an amino acid sequence which is at least 52 % identical to PS; (b) comprising a 1018 (S1) or 837 (S8) nucleotide sequence, fully defined in the specification; (c) which hybridizes under stringent conditions to an above mentioned polynucleotide; (d) having a sequence which deviates from the above mentioned sequences due to degeneracy of genetic code; or (e) which represents a fragment, derivative or allelic variant of the above mentioned polynucleotide sequences; (2) an expression vector (III) containing (II); (3) a host cell (IV) containing (III); (4) a substantially purified esp 1-like polypeptide (P1) encoded by (II); (5) preparation of (I), comprising **culturing** (IV) under expression conditions, and recovering the polypeptide; (6) a reagent (V) that modulates the activity of (I) or (II), which is identified by screening methods involving (P1) or (I), or (II); (7) a diagnostic kit for detecting a coding sequence for a polypeptide comprising an amino acid sequence of PS, comprising a polynucleotide having 11 contiguous nucleotides of (S1) or (S8) and instructions of carrying out the detection method; (8) a kit for detecting a polypeptide comprising an amino acid sequence of PS, comprising an antibody which specifically binds to (I) and instructions for carrying out the method; (9) a pharmaceutical composition (VI) comprising (III) or (V) which specifically binds to (I) having an amino acid sequence of

PS, or to (II) and modulates their activity, identified by screening methods involving (P1) or (I), or (II); and a carrier; (10) a fusion protein comprising (I); (11) screening (M1) for agents which modulate an activity of a human esp 1-like enzyme comprising contacting a test compound with a product encoded by a polynucleotide which comprises the nucleotide sequence of (S1) or (S8) and detecting binding of the test compound of the product, where a test compound which binds to the product is identified as a potential agent for regulating the activity of the human esp 1-like enzyme; (12) reducing (M2) activity of human esp 1-like enzyme comprising contacting a cell with a reagent which specifically binds to a product encoded by a polynucleotide comprising the nucleotide sequence of (S1) or (S8); and (13) a pharmaceutical composition comprising a reagent which binds to a product of a polynucleotide comprising the nucleotide sequence of (S1) or (S8) and a carrier.

WIDER DISCLOSURE - Antibodies against (I) are disclosed as new.

BIOTECHNOLOGY - Preferred Polynucleotide: (II) is a cDNA molecule having a sequence of (S1) or (S8), and encoding an amino acid sequence of PS. Preferred Polypeptide: (I) consists of an amino acid sequence of PS. Preferred Method: The product encoded by (II) which is contacted with test compound is a polypeptide or RNA. In (M2), if the product is polypeptide, then the reagent employed for reducing the activity of human esp 1-like enzyme is an antibody, and if the product is an RNA, then the reagent used is ribozyme or an antisense oligonucleotide. The reagent is contacted with cell in vivo or in **vitro.**

ACTIVITY - Antiinflammatory; antiasthmatic; antiallergic; osteopathic; cytostatic; dermatological. Synthesis of an antisense esp 1-like enzyme oligonucleotide comprising at least 11 contiguous nucleotides from the complement of a 1018 nucleotide sequence, fully in the specification was performed on a Pharmacia Gene Assembler series synthesizer. Following assembly and deprotection, the oligonucleotide was twice ethanol-precipitated, dried and suspended in phosphate-buffered saline (PBS) at the desired concentration. Purity of the oligonucleotides was tested by capillary gel electrophoresis and ion exchange high performance liquid chromatography (HPLC). The endotoxin level in the oligonucleotide preparation was determined using the Limulus Amebocyte assay. An aqueous composition containing the antisense oligonucleotide at a concentration of 0.1-100 micro-m was administered directly to a patient having asthma by injection. The severity of the patient's asthma was decreased.

MECHANISM OF ACTION - esp 1-like enzyme activity modulator.

USE - (I) is useful for screening for agents which decrease the activity of an esp 1-like enzyme which involves contacting a test compound with (P1) or (II), and detecting binding of test compound to polypeptide or polynucleotide. The test compound which binds to the polypeptide or polynucleotide is identified as a potential therapeutic agent for decreasing the activity of esp 1-like enzyme. (I) is also useful for screening for agents which regulate the activity of an esp 1-like enzyme. The method involves contacting a test compound with (P1) or (I) and detecting the esp 1-like

enzyme activity of the polypeptide. The test compound which increases or decreases the esp 1-like enzyme activity is identified as a potential therapeutic for increasing or decreasing the esp 1-like enzyme activity. The method optionally involves detecting binding of the test compound to the polypeptide and a test compound which binds to the polypeptide is identified as a potential agent for regulating activity of the human esp 1-like enzyme. The polypeptide is contacted with the test compound in a cell, in **vitro** or in a cell-free system. Either the polypeptide or the test compound comprises a detectable label and the test compound when binding to the polypeptide displaces the labeled ligand bound to the polypeptide. Also, the polypeptide or the test compound is bound to a solid support. (II) is useful for detecting a polynucleotide which encodes (I) in a biological sample which involves hybridizing a polynucleotide comprising 11 contiguous nucleotides of (S1) or (S8) to a nucleic acid material of a biological sample, thereby forming a hybridization complex and detecting a hybridization complex. Before hybridization the nucleic acid material of the biological sample is amplified. (V) is useful for detecting (P1) or (II) which involves contacting a biological sample with (V). (V) is also useful for reducing the activity of esp 1-like enzyme which involves contacting a cell with (V) which binds to (II) or (P1). (V) (an antibody is useful for detecting the polypeptide having an amino acid sequence of PS. (V) is also useful for treating a esp 1-like enzyme dysfunction related diseases condition such as asthma, chronic obstructive pulmonary disease, airway allergy or osteoporosis. (VI) is useful for modulating esp 1-like enzyme activity in a disease condition as mentioned above. (All claimed). (I) is useful in diagnostic assays for detecting diseases and abnormalities or susceptibility to diseases and abnormalities related to presence of mutations in the nucleic acid sequences which encode the enzyme. (V) is also useful for treating dermatitis, Paget's disease, and preventing degradation of bone implants particularly dental implants.

ADMINISTRATION - Pharmaceutical compositions comprising (I), (II) or (V) are administered by oral, intravenous, intramuscular, intraperitoneal, or parenteral route. Dosage of (V) ranges from 0.1-100000 micro-g. In vivo dosages of an antibody (i.e. (V)) range from 5-50 micro-g/kg. Polynucleotides encoding single chain antibodies are administered in dosages ranging from 100-200 ng.

EXAMPLE - Polymerase chain reaction (PCR) amplification of human **eosinophil** serine protease (ESP) 1-like enzyme gene from human trachea cDNA library results in 3 PCR products. Cloning and sequence analysis of the three PCR products showed that ESP 1-like enzyme gene has three splicing variants with the sequences slightly different from previously identified. The existence of the splicing variants was confirmed by using primers covering the sequences of splicing junction. ESP 1-like enzyme and its variants, namely ESP-1-L-L, ESP-1-L-M, and ESP-1-L-S, encode polypeptides containing 334, 305 and 259 amino acids, respectively. All these splicing forms contained the triad catalytic domains. However the hydrophobic region of the N-terminal signal sequence in ESP 1-L-S was partially deleted, indicating that ESP-1-L-S has a cytoplasmic localization. ESP-1-like enzyme genes have less than 50 % identity with ESP-1, a serine

protease identified from **eosinophils.** High homologies were observed in N-terminal signal sequence, three serine protease catalytic domains and a hydrophobic tails. Based on database searches and computer-assisted multiple sequence alignments and phylogenetic comparisons, in addition to the similarity with ESP-1, ESP-1-like enzyme amino acid sequences were most similar to the well-characterized tryptases, such as mouse tryptase 4, human tryptase alpha, beta, gamma and protasin. ESP 1-like enzyme has the particularly tryptic-like serine protease structure features, e.g. the catalytic triad residue His (94 for ESP-1-L-L), Asp (163 for ESP-1-L-L) and Ser (265 for ESP-1-L-L). Features shared with tryptase gamma, prostatin and ESP-1 include Cys62 and Cys183. However, the ending of the Arg of a propeptide was not existed in ESP 1-like. In addition, LeuProProProTyr motif for oligomerization identified in tryptase beta is conserved in the ESP-1-like enzyme. Therefore both mechanisms involved in activation of tryptase-like serine proteases are employed by ESP-1-like enzyme. ESP-1-like enzyme was expressed as a membrane protease and expression of ESP-1-like enzyme induces protease activity in membrane fraction. Recombinant ESP-1-like-enzyme-V5-His was expressed in A549 cells. Immunostaining of A549 cells and immunoblotting of fractional cell lysates with anti-V5 antibodies showed that ESP 1-like enzyme was expressed as a membrane protein. When the membrane fractions from ESP 1-like enzyme expressing A549 cells were subjected to protease assay with a panel of peptide structures, cleavages were observed with the following peptides. Suc-Ala-Ala-Pro-Phe-MCA (chymotrypsin), Pro-Phe-Arg-MCA (Kallikrein), Boc-Glu-Ala-Arg-MCA (Trypsin) and Boc-Phe-Ser-Arg-MCA (Tryptase). These substrates were not active with the membrane fractions prepared from A549 cells transfected with the mock vectors. Therefore, the protease activities in the membrane fraction of ESP-1-like enzyme expressing A549 cells were contributed either directly by ESP-1-like enzyme itself or by ESP-1-like-activated proteases. Further experiment carried out showed that ESP-1-like enzyme is secreted from cells after proteolysis in the inflammed tissue and functions as inflammatory mediators involving in airway damage and remodeling. Greatly increased expression of ESP-1-like enzyme was bronchial endothelial cells by **interleukin** (IL)-4, CD40 and tumor necrosis factor (TNF)-alpha stimulation showed that ESP-1-like enzyme serine protease plays pivotal roles in inflammation-induced endothelium leakage, plasma exudation, mucus production, tissue swelling, and infiltration of leukocytes. The induced expression was also observed in bronchial epithelial cells, indicating that ESP-1-like enzyme may involve in damaging and shedding of epithelium. (131 pages)

CLASSIFICATION: THERAPEUTICS, Protein Therapeutics; GENETIC TECHNIQUES and APPLICATIONS, Gene Expression Techniques and Analysis; DISEASE, Respiratory System; DISEASE, Other Diseases; DIAGNOSTICS, Molecular Diagnostics; THERAPEUTICS, Gene Therapy

CONTROLLED TERMS: HUMAN RECOMBINANT **EOSINOPHIL** SERINE PROTEASE PREP., ISOL., VECTOR-MEDIATED GENE TRANSFER, EXPRESSION IN HOST CELL, ANTIBODY, RIBOZYME, ANTISENSE OLIGONUCLEOTIDE, APPL. **DRUG SCREENING** ASTHMA, PULMONARY DISEASE, AIRWAY ALLERGY,OSTEOPOROSIS, PAGET DISEASE, INFLAMMATION

Searched by Barb O'Bryen, STIC 2-2518

DIAGNOSIS, THERAPY, GENE THERAPY ANIMAL MAMMAL RNA ENZYME DNA SEQUENCE PROTEIN SEQUENCE (21, 23)

FILE 'HOME' ENTERED AT 15:14:28 ON 28 SEP 2006

```
L84           0 SEA ABB=ON  (L75 OR L76) AND L69
L85          40 SEA ABB=ON  (L75 OR L76) AND L80
L86          18 SEA ABB=ON  (L75 OR L76) AND L80 AND (L77 OR L78 OR L79)
                D TRIAL 1-18
L87           1 SEA ABB=ON  L86 AND DEGRANULAT?/BI,ABEX

     FILE 'STNGUIDE' ENTERED AT 14:19:21 ON 28 SEP 2006

     FILE 'DRUGU, JICST-EPLUS, PASCAL, BIOTECHNO, BIOSIS, ESBIOBASE,
     BIOTECHDS, CONFSCI, DISSABS, SCISEARCH' ENTERED AT 14:24:23 ON 28 SEP 2006
L88          60 SEA ABB=ON  PONIKAU J?/AU
L89        4318 SEA ABB=ON  KITA H?/AU
L90         173 SEA ABB=ON  SHERRIS D?/AU
L91       85103 SEA ABB=ON  EOSINOPHIL#
L92      115320 SEA ABB=ON  (DRUG# OR COMPOUND#)(2A)(SCREEN? OR EVALUAT? OR
                DISCOVER?)
L93        1652 SEA ABB=ON  FUNG##(2A) ANTIGEN#
L94      281222 SEA ABB=ON  ALTERNARIA OR CANDIDA OR ASPERGILLUS OR CLADOSPORI?

L95          28 SEA ABB=ON  L88 AND L89 AND L90 AND (L91 OR L92 OR L93 OR L94)

L96           0 SEA ABB=ON  L91 AND L92 AND (L93 OR L94)
L97     2596477 SEA ABB=ON  VITRO
L98     2951687 SEA ABB=ON  CULTUR?
L99          61 SEA ABB=ON  L91 AND L92 AND (L97 OR L98)
L100      26327 SEA ABB=ON  DEGRANULAT?
L101       3600 SEA ABB=ON  MAJOR BASIC
L102      55262 SEA ABB=ON  NEUROTOXIN#
L103       9491 SEA ABB=ON  CATIONIC PROTEIN#
L104     218360 SEA ABB=ON  PEROXIDASE# OR PER OXIDASE#
L105     619518 SEA ABB=ON  CYTOKINE#
L106     628138 SEA ABB=ON  INTERLEUKIN# OR IL5 OR IL8 OR IL13 OR (IL(W)(5 OR
                8 OR 13))
L107         16 SEA ABB=ON  L99 AND (L100 OR L101 OR L102 OR L103 OR L104 OR
                L105 OR L106)

     FILE 'STNGUIDE' ENTERED AT 14:30:23 ON 28 SEP 2006

     FILE 'DRUGU, JICST-EPLUS, PASCAL, BIOTECHNO, BIOSIS, ESBIOBASE,
     BIOTECHDS, CONFSCI, DISSABS, SCISEARCH' ENTERED AT 14:31:17 ON 28 SEP 2006
                D QUE L95

     FILE 'MEDLINE' ENTERED AT 14:31:36 ON 28 SEP 2006
                D QUE L21

     FILE 'EMBASE' ENTERED AT 14:31:37 ON 28 SEP 2006
                D QUE L55

     FILE 'WPIX' ENTERED AT 14:31:37 ON 28 SEP 2006
                D QUE L69

     FILE 'CAPLUS' ENTERED AT 14:31:38 ON 28 SEP 2006
                D QUE L1
                D QUE L17
L108          6 SEA ABB=ON  (L1 OR L17)

     FILE 'STNGUIDE' ENTERED AT 14:32:29 ON 28 SEP 2006

     FILE 'CAPLUS, MEDLINE, WPIX, EMBASE, DRUGU, PASCAL, BIOSIS, ESBIOBASE,
     SCISEARCH' ENTERED AT 15:10:41 ON 28 SEP 2006
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     FILE 'WPIX' ENTERED AT 13:09:08 ON 28 SEP 2006
L66           4 SEA ABB=ON  PONIKAU J?/AU
L67         338 SEA ABB=ON  KITA H?/AU
L68           9 SEA ABB=ON  SHERRIS D?/AU
L69           3 SEA ABB=ON  L66 AND L67 AND L68
                D TRIAL 1-3

     FILE 'STNGUIDE' ENTERED AT 13:10:02 ON 28 SEP 2006

     FILE 'LWPI' ENTERED AT 13:12:45 ON 28 SEP 2006
                E B04-B04C1+ALL/MC
                E B04-F02+ALL/MC
                E  B04-F04+ALL/MC
                E B04-F09+ALL/MC
                E B04-F09A+ALL/MC
                E  B04-P01A+ALL/MC
                E B11-C08E+ALL/MC
                E B12-K04+ALL/MC
                E B12-K04E+ALL/MC
                E B14-A04+ALL/MC
                E B14-A04A+ALL/MC
                E B14-C03+ALL/MC
                E B14-G02A+ALL/MC
                E D05-H05+ALL/MC
                E D05-H08+ALL/MC
                E D05-H09+ALL/MC
                E D05-H13+ALL/MC
                E S03-E14H+ALL/MC
                E S03-E14H4+ALL/MC

     FILE 'STNGUIDE' ENTERED AT 13:13:13 ON 28 SEP 2006

     FILE 'LWPI' ENTERED AT 13:17:53 ON 28 SEP 2006
                E B14-A04+ALL/MC
                E B04-F09+ALL/MC

     FILE 'WPIX' ENTERED AT 13:18:37 ON 28 SEP 2006
L70        2449 SEA ABB=ON  B04-B02B2/MC OR B14-A04A/MC OR B04-F09A/MC OR
                B14-A04B/MC
L71        1446 SEA ABB=ON  C04-B02B2/MC OR C14-A04A/MC OR C04-F09A/MC OR
                C14-A04B/MC
L72       14625 SEA ABB=ON  ALTERNARIA/BI,ABEX OR CANDIDA/BI,ABEX OR ASPERGILLU
                S/BI,ABEX OR CLADOSPORI?/BI,ABEX
L73         199 SEA ABB=ON  FUNG##/BI,ABEX(2A)ANTIGEN#/BI,ABEX
L74        4445 SEA ABB=ON  B04-B04C1/MC OR C04-B04C1/MC
L75        6417 SEA ABB=ON  DRUG#/BI,ABEX(2A)(SCREEN?/BI,ABEX OR DISCOVER?/BI,A
                BEX OR EVALUAT?/BI,ABEX)
L76        5060 SEA ABB=ON  B12-K04E1/MC OR C12-K04E1/MC
L77      112165 SEA ABB=ON  CULTUR?/BI,ABEX
L78       28520 SEA ABB=ON  VITRO/BI,ABEX
L79       39006 SEA ABB=ON  D05-H08/MC
L80        1087 SEA ABB=ON  EOSINOPHIL#/BI,ABEX
L81           2 SEA ABB=ON  L80 AND (L70 OR L71 OR L72 OR L73 OR L74) AND (L75
                OR L76)
                D TRIAL 1-2
                D TRIAL L69 1-3
                D AB 2 L69
L82           3 SEA ABB=ON  L80 AND L69
L83           2 SEA ABB=ON  (L70 OR L71 OR L72 OR L73 OR L74) AND L69
                D SCAN
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L36           3 SEA ABB=ON  L33 AND L35 AND L27
L37      337882 SEA ABB=ON  IN VITRO/CT
L38           4 SEA ABB=ON  L22 AND L27 AND L37
L39      799287 SEA ABB=ON  CELLS, CULTURED+NT/CT
L40           5 SEA ABB=ON  L39 AND L22 AND L27
L41           9 SEA ABB=ON  (L36 OR L38 OR L40)

     FILE 'EMBASE' ENTERED AT 12:52:51 ON 28 SEP 2006
L42          20 SEA ABB=ON  PONIKAU J?/AU
L43         410 SEA ABB=ON  KITA H?/AU
L44          59 SEA ABB=ON  SHERRIS D?/AU
                E EOSINOPHIL+NT/CT
                E EOSINOPHIL+LL/CT
                E EOSINOPHIL+ALL/CT
L45       13763 SEA ABB=ON  EOSINOPHIL/CT
L46       74633 SEA ABB=ON  DRUG SCREENING/CT
                E FUNGUS ANTIGEN/CT
                E E3+ALL
L47        1358 SEA ABB=ON  FUNGUS ANTIGEN/CT
L48         280 SEA ABB=ON  CANDIDA ANTIGEN/CT
                E CANDIDA+NT/CT
L49       29141 SEA ABB=ON  CANDIDA+NT/CT
                E ALTERNARIA+ALL/CT
L50        1107 SEA ABB=ON  ALTERNARIA/CT
L51       17660 SEA ABB=ON  ASPERGILLUS+NT/CT
                E CLADOSPO/CT
                E CLADOSPOR/CT
                E CLADOSPORIUM/CT
                E E3+ALL
L52         937 SEA ABB=ON  CLADOSPORIUM+NT/CT
                E ALTERNARIA ANT/CT
L53           1 SEA ABB=ON  ALTERNARIA ANTIGEN/CT
                E ASPERGILLUS ANT/CT
L54           3 SEA ABB=ON  ASPERGILLUS ANTIGEN/CT
                E CLADOSPORIUM ANT/CT
                E E4+ALL
L55          10 SEA ABB=ON  L42 AND L43 AND L44
                D TRIAL 1-5
L56           0 SEA ABB=ON  L45 AND L46 AND (L47 OR L48 OR L49 OR L50 OR L51
                OR L52 OR L53 OR L54)

     FILE 'STNGUIDE' ENTERED AT 12:58:17 ON 28 SEP 2006

     FILE 'EMBASE' ENTERED AT 13:03:17 ON 28 SEP 2006
L57          54 SEA ABB=ON  L45 AND L46
                D TRIAL 1-10
L58          15 SEA ABB=ON  L45/MAJ AND L46
L59           4 SEA ABB=ON  L45/MAJ AND L46/MAJ
                D TRIAL 1-4
L60      592822 SEA ABB=ON  IN VITRO STUDY/CT
L61           8 SEA ABB=ON  L45 AND L46 AND L60
L62       33829 SEA ABB=ON  CELL SURVIVAL/CT
L63       25386 SEA ABB=ON  CELL VIABILITY/CT
                E CULTURED CELLS+ALL/CT
                E CELLS, CULTURED+ALL/CT
                E E2+ALL
                E E38+ALL
L64      273163 SEA ABB=ON  CELL CULTURE+NT/CT
L65           3 SEA ABB=ON  L45 AND L46 AND (L62 OR L63 OR L64)
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=> ******SEARCH HISTORY*****


=> d his nofile

     (FILE 'HOME' ENTERED AT 12:28:55 ON 28 SEP 2006)

     FILE 'CAPLUS' ENTERED AT 12:29:05 ON 28 SEP 2006
                E US2005-505379/APPS
L1            1 SEA ABB=ON  US2005-505379/AP
                D SCAN
L2        48797 SEA ABB=ON  SCREENING/CW
                E EOSINOPHIL+ALL/CT
L3        11144 SEA ABB=ON  EOSINOPHIL?/CW
L4          139 SEA ABB=ON  ANTIGENS/CT(L)FUNG##/OBI
L5         1185 SEA ABB=ON  ALTERNARIA/CT
L6         5410 SEA ABB=ON  CANDIDA/CT
L7         7743 SEA ABB=ON  ASPERGILLUS/CT
L*** DEL      0 S CLADISPORIUM/CT
L8          908 SEA ABB=ON  CLADOSPORIUM/CT
L9            1 SEA ABB=ON  L2 AND L3 AND (L4 OR L5 OR L6 OR L7 OR L8)
L10          18 SEA ABB=ON  L3 AND (L4 OR L5 OR L6 OR L7 OR L8)
                D SCAN

     FILE 'STNGUIDE' ENTERED AT 12:34:50 ON 28 SEP 2006

     FILE 'CAPLUS' ENTERED AT 12:39:48 ON 28 SEP 2006
L11       10169 SEA ABB=ON  EOSINOPHIL+OLD/CT
L12      328218 SEA ABB=ON  DRUG#/CW
L13           8 SEA ABB=ON  (L2 OR L12) AND L11 AND (L4 OR L5 OR L6 OR L7 OR
                L8)
                D SCAN TI
L14          10 SEA ABB=ON  PONIKAU J?/AU
L15        1790 SEA ABB=ON  KITA H?/AU
L16          29 SEA ABB=ON  SHERRIS D?/AU
L17           6 SEA ABB=ON  L14 AND L15 AND L16

     FILE 'MEDLINE' ENTERED AT 12:41:21 ON 28 SEP 2006
L18          18 SEA ABB=ON  PONIKAU J?/AU
L19         396 SEA ABB=ON  KITA H?/AU
L20          69 SEA ABB=ON  SHERRIS D?/AU
L21           9 SEA ABB=ON  L18 AND L19 AND L20
                D TRIAL 1-9
L22       15753 SEA ABB=ON  EOSINOPHILS/CT
L23         930 SEA ABB=ON  ALTERNARIA/CT
L24       24899 SEA ABB=ON  CANDIDA+NT/CT
L25       17352 SEA ABB=ON  ASPERGILLUS+NT/CT
L26         779 SEA ABB=ON  CLADOSPORIUM/CT
L27       94158 SEA ABB=ON  DRUG EVALUATION, PRECLINICAL+NT/CT
L28          33 SEA ABB=ON  L22 AND L27
L29           0 SEA ABB=ON  L22 AND L27 AND (L23 OR L24 OR L25 OR L26)
L30        4570 SEA ABB=ON  ANTIGENS, FUNGAL+NT/CT
L31           0 SEA ABB=ON  L22 AND L27 AND L30
L32           0 SEA ABB=ON  L22 AND L27 AND (L23 OR L24 OR L25 OR L26 OR L30)
                D TRIAL L28 1-8
L33        2219 SEA ABB=ON  L22(L)DE/CT
L34          16 SEA ABB=ON  L33 AND L27
                D TRIAL 1-16
L35        1509 SEA ABB=ON  L22(L)CY/CT
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L109          17 DUP REM L108 L21 L69 L55 L95 (39 DUPLICATES REMOVED)
                        ANSWERS '1-6' FROM FILE CAPLUS
                        ANSWERS '7-11' FROM FILE MEDLINE
                        ANSWER '12' FROM FILE WPIX
                        ANSWER '13' FROM FILE EMBASE
                        ANSWERS '14-16' FROM FILE BIOSIS
                        ANSWER '17' FROM FILE SCISEARCH
                  D IBIB ED ABS 1-17

     FILE 'CAPLUS' ENTERED AT 15:11:17 ON 28 SEP 2006
                  D QUE L13
L110           7 SEA ABB=ON  L13 NOT (L1 OR L17)

     FILE 'MEDLINE' ENTERED AT 15:11:24 ON 28 SEP 2006
                  D QUE L32
                  D QUE L36
                  D QUE L38
                  D QUE L40
L111           9 SEA ABB=ON  (L36 OR L38 OR L40) NOT L21

     FILE 'EMBASE' ENTERED AT 15:12:54 ON 28 SEP 2006
                  D QUE L56
                  D QUE L61
                  D QUE L65
L112          11 SEA ABB=ON  (L61 OR L65) NOT L55

     FILE 'WPIX' ENTERED AT 15:12:55 ON 28 SEP 2006
                  D QUE L81
                  D QUE L87
L113           3 SEA ABB=ON  (L81 OR L87) NOT L69

     FILE 'DRUGU, JICST-EPLUS, PASCAL, BIOTECHNO, BIOSIS, ESBIOBASE,
     BIOTECHDS, CONFSCI, DISSABS, SCISEARCH' ENTERED AT 15:12:59 ON 28 SEP 2006
                  D QUE L96
                  D QUE L107
L114          16 SEA ABB=ON  L107 NOT L95

     FILE 'STNGUIDE' ENTERED AT 15:13:15 ON 28 SEP 2006

     FILE 'CAPLUS, MEDLINE, WPIX, EMBASE, DRUGU, PASCAL, BIOTECHNO, BIOSIS,
     ESBIOBASE, BIOTECHDS, SCISEARCH' ENTERED AT 15:13:36 ON 28 SEP 2006
L115          42 DUP REM L110 L111 L113 L112 L114 (4 DUPLICATES REMOVED)
                        ANSWERS '1-7' FROM FILE CAPLUS
                        ANSWERS '8-16' FROM FILE MEDLINE
                        ANSWERS '17-19' FROM FILE WPIX
                        ANSWERS '20-30' FROM FILE EMBASE
                        ANSWER '31' FROM FILE DRUGU
                        ANSWER '32' FROM FILE PASCAL
                        ANSWERS '33-42' FROM FILE BIOTECHDS
                  D IBIB ED ABS HITIND 1-7
                  D IALL 8-16
                  D IALL ABEQ TECH 17-19
                  D IALL 20-42

     FILE 'HOME' ENTERED AT 15:14:28 ON 28 SEP 2006

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